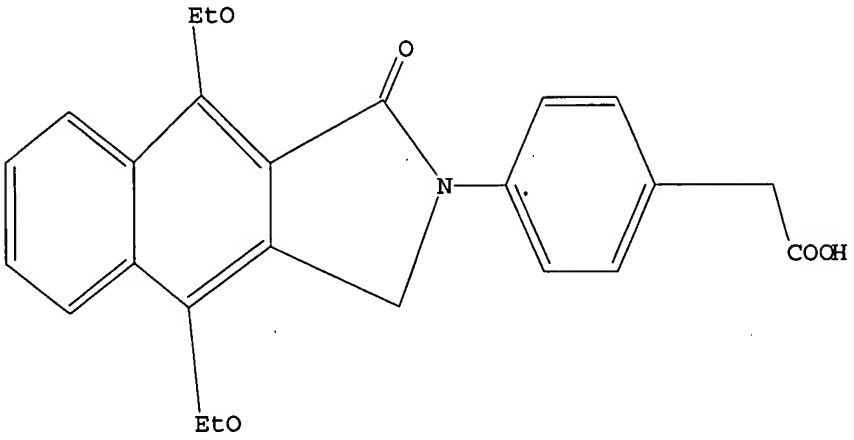
9/28/03

L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1
SAMPLE SEARCH INITIATED 21:08:34 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 10 TO ITERATE

100.0% PROCESSED 10 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 11 TO 389
PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 21:08:52 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 155 TO ITERATE

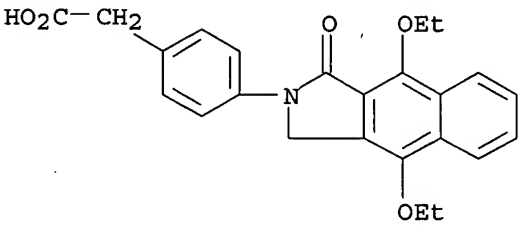
100.0% PROCESSED 155 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

L3 2 SEA SSS FUL L1

=> d l3 1-2

L3 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2003 ACS on STN
RN 449764-07-2 REGISTRY
CN Benzeneacetic acid, 4-(4,9-diethoxy-1,3-dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C24 H21 N O6
SR CA
LC STN Files: CA, CAPLUS

3 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS on STN
RN 325780-75-4 REGISTRY
CN Benzeneacetic acid, 4-(4,9-diethoxy-1,3-dihydro-1-oxo-2H-benz[f]isoindol-2-yl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C24 H23 N O5
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



elected piece allowable?

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> fil caplus uspatfull medline embase biosis

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	152.71	154.39

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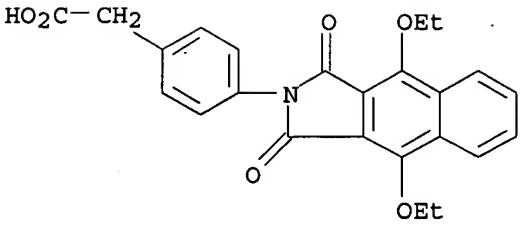
=> s 325780-75-4/rn
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L4 3 325780-75-4/RN

=> d l4 1-3 ab bib kwic

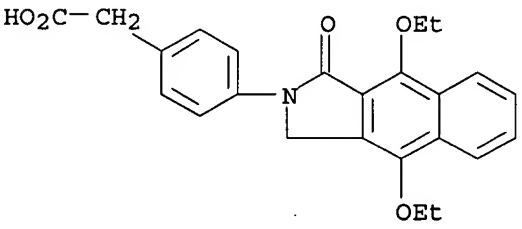
L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN
AB The title compds. [I; R1 = H, halo, alkyl, etc.; R2 = alkyl; R3 = H, O; R4 = H, alkyl; R5 = alkyl (un)substituted Ph, naphthyl, etc.; R7-R10 = H, alkyl, alkoxy, etc.; R11 = H, OH, halo, etc.] which bind with high affinity to the EP4 receptor and are of use in the treatment or prevention of conditions such as a pain, inflammatory, immunol., bone, neurodegenerative or renal disorder, were prepd. E.g., a multi-step synthesis of II which showed pKb of 7.0 or greater in EP4 antagonist



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS on STN
RN 325780-75-4 REGISTRY
CN Benzeneacetic acid, 4-(4,9-diethoxy-1,3-dihydro-1-oxo-2H-benz[f]isoindol-2-yl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C24 H23 N O5
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)

assay, was given.
AN 2002:487529 CAPLUS
DN 137:63174
TI Preparation of benzo[f]isoindoles as EP4 receptor ligands
IN Giblin, Gerard Martin Paul; Frye, Stephen Vernon; Roomans, Susan
PA Glaxo Group Limited, UK
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002050033	A1	20020627	WO 2001-GB5706	20011220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002017287	A5	20020701	AU 2002-17287	20011220
EP 1343759	A1	20030917	EP 2001-271356	20011220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI GB 2000-31295	A	20001221		
WO 2001-GB5706	W	20011220		

OS MARPAT 137:63174
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT 59883-07-7P 59883-08-8P **325780-75-4P** 325780-76-5P
325780-77-6P 325780-78-7P 325780-79-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of benzo[f]isoindoles as EP4 receptor ligands)

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN
AB The invention discloses the use of an EP4 receptor agonist and pharmaceutically acceptable derivs. thereof for the manuf. of a medicament for the treatment of neuropathic pain, excluding use of [4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid and pharmaceutically acceptable derivs. thereof.
AN 2002:465800 CAPLUS
DN 137:28310
TI Use of EP4 receptor agonists for treating neuropathic pain
IN Foord, Steven Michael; Giblin, Gerard Martin Paul; Wilson, Richard John
PA Glaxo Group Limited, UK
SO PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002047669	A1	20020620	WO 2001-GB5501	20011213
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,				

CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002022191 A5 20020624 AU 2002-22191 20011213

PRAI GB 2000-30541 A 20001214

WO 2001-GB5501 W 20011213

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT **325780-75-4**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(EP4 receptor agonists for treatment of neuropathic pain)

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN

AB The present invention relates to the use of an EP4 receptor ligand in the manuf. of a medicament for use in the treatment of neuropathic pain, colon cancer, migraine, and for increasing the latency of HIV infection. An example compd. (I) was prepd.

AN 2001:114969 CAPLUS

DN 134:157579

TI Use of EP4 receptor ligands in the treatment of, interalia, neuropathic pain and colon cancer

IN Clayton, Nicholas Maughan; Collins, Susanne Denise; Foord, Steven Michael; Giblin, Gerard Martin Paul

PA Glaxo Group Limited, UK

SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001010426	A2	20010215	WO 2000-EP7669	20000808
WO 2001010426	A3	20011220		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1202730	A2	20020508	EP 2000-956408	20000808

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL

JP 2003506404	T2	20030218	JP 2001-514946	20000808
PRAI GB 1999-18745	A	19990810		
GB 1999-28437	A	19991201		
WO 2000-EP7669	W	20000808		

IT **325780-75-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(EP4 receptor ligands in the treatment of, inter alia, neuropathic pain and colon cancer)

=>

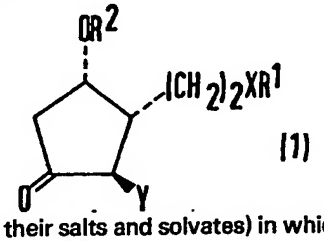
(12) UK Patent Application (19) GB (11) 2 075 503 A

(21) Application No 8113239
(22) Date of filing 29 Apr 1981
(30) Priority data
(31) 80/14256
(32) 30 Apr 1980
(31) 81/00326
(32) 7 Jan 1981
(33) United Kingdom (GB)
(43) Application published 18 Nov 1981
(51) INT CL³ C07D 295/10 A61K 31/557 C07D 279/34 413/12//C07C 33/24 43/20 69/76 C07D 333/06 (C07D 413/12 295/10 333/06)
(52) Domestic classification C2C 1175 1510 1532 1562 1582 1737 200 202 215 216 220 221 222 225 226 227 22Y 246 248 250 251 254 255 256 259 25Y 28X 292 29X 29Y 30Y 313 314 31Y 338 339 348 350 351 353 357 360 361 362 364 366 367 368 36Y 373 37X 37Y 389 400 409 40Y 43X 440 464 490 491 500 503 509 50Y 613 623 624 625 628 633 634 638 644 652 658 65X 662 668 66X 699 774 777 778 779 802 80Y AA BG BL BT QN QT TA UF WH WL WR YX
(56) Documents cited GB 2028805
(58) Field of search C2C

(71) Applicant Glaxo Group Limited, Clarges House, 6-12, Clarges Street, London W1Y 8DH
(72) Inventors Eric William Collington, Peter Hallett, Christopher John Wallis, John Bradshaw, Norman Frank Hayes
(74) Agent Frank B. Dehn & Co., Imperial House, 15/19, Kingsway, London WC2B 6UZ

(54) **Prostanoid Aminocyclopentane Alkenoic Acids and Esters and Their Preparation and Pharmaceutical Formulation**

(57) Compounds are described of the formula



(1)

(and their salts and solvates) in which:

X is cis or trans —CH=CH—;

R^1 is C_{1-7} alkyl terminated by —$COOR^3$ where R^3 is H, C_{1-6} alkyl or C_{7-10} aralkyl;

Y is a saturated heterocyclic amino group having 5—8 ring members; and

R^2 is C_{2-4} alkanoyl, C_{3-6} alkenyl (optionally substituted), C_{1-12} alkyl, or substituted or unsubstituted phenylalkyl, thienylalkyl, furanylalkyl, biphenylalkyl or naphthylalkyl.

These compounds inhibit blood platelet aggregation and bronchoconstriction and may be formulated for use as antithrombotic and anti-asthmatic agents.

GB 2 075 503 A

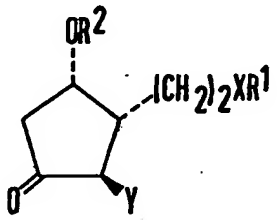
SPECIFICATION

Aminocyclopentane Alkenoic Acids and Esters and Their Preparation and Pharmaceutical Formulation

The endoperoxides prostaglandins G_2 and H_2, and thromboxane A_2 are naturally occurring, reactive metabolites of arachidonic acid in human platelets. They are not only potent aggregatory agents but are also constrictors of vascular and bronchial smooth muscle, and therefore substances which antagonise their effects are of considerable interest in human medicine.

We have now found a new group of compounds which have shown endoperoxide and thromboxane antagonist activity, and are therefore of interest in the treatment of asthma and cardiovascular diseases. These compounds can broadly be described as cyclopentanealkenoic acids and esters in which the double bond is in the 3,4-position in relation to the cyclopentane ring and in which the ring is substituted by heterocyclic amino, oxo and alkanoyloxy or ether (particularly aralkoxy) groups.

The invention thus provides compounds of the general formula (1)



(1)

wherein

X is cis or trans —CH=CH—;

R^1 is straight or branched C_{1-7} alkyl bearing as a terminal substituent —$COOR^3$ where R^3 is a hydrogen atom, C_{1-6} alkyl or C_{7-10} aralkyl (e.g. benzyl);

Y represents a saturated heterocyclic amino group which has 5—8 ring members and (a) optionally contains in the ring —O—, —S—, —SO_2—, —NR^4 (where R^4 is a hydrogen atom, C_{1-7} alkyl or aralkyl having a C_{1-4} alkyl portion); and/or (b) is optionally substituted by one or more C_{1-4} alkyl groups;

R^2 is (i) C_{2-4} alkanoyl; (ii) C_{3-6} alkenyl, optionally substituted by phenyl (the phenyl being optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{5-7} cycloalkyl or phenyl (C_{1-4}) alkyl), biphenyl (optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy or halogen), or naphthyl; (iii) C_{1-12} alkyl; (IV) C_{1-5} alkyl substituted by (a) phenyl [optionally substituted by halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-4} hydroxyalkoxy, trifluoromethyl, cyano, aryloxy (e.g. phenoxy), C_{5-7} cycloalkyl, aralkoxy (e.g. benzyloxy), dimethylaminomethyl, carboxamido (—$CONH_2$), thiocarboxamido (—$CSNH_2$), C_{1-4} alkanoyl, —NR^5R^6 (where R^5 and R^6 are the same or different and are each a hydrogen atom or C_{1-4} alkyl, or where —NR^5R^6 is a saturated heterocyclic amino group as defined above for Y), C_{1-3} alkylthio, C_{1-3} alkylsulphinyl, C_{1-3} alkylsulphonyl, phenylalkyl having a C_{1-3} alkyl portion, aminosulphonyl, C_{1-3} alkanoylaminosulphonyl, phenylsulphonyl (the phenyl portion being optionally substituted by C_{1-3} alkyl or C_{1-3} alkoxy), nitro, or thienyl], (b) thienyl or furanyl [the thienyl and furanyl groups being optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, aryl (e.g. phenyl) or phenyl (C_{1-3}) alkyl or phenyl (C_{1-3})-alkoxy (the aryl or phenyl group in each case being optionally substituted by C_{1-3} alkyl, C_{1-3} alkoxy or halogen), aryloxy (e.g. phenoxy, C_{5-7} cycloalkyl, halogen, nitro or thienyl], (c) biphenyl (optionally substituted by phenyl or one or two C_{1-4} alkyl, C_{1-4} alkoxy or halogen substituents), or (d) naphthyl (optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy or halogen);

and the physiologically acceptable salts and the solvates (e.g. hydrates) thereof.

The structural formulae herein are to be understood to include the enantiomers of each of the compounds concerned as well as mixtures of the enantiomers, including racemates, even though the precise structure as set out only relates to one enantiomer.

The alkyl groups referred to above in the definition of the compounds of formula (1) may be straight or branched.

The alkyl portion of the group R^1 may for example contain 1—5 carbon atoms in a straight or branched chain, and is preferably —CH_2CH_2—. Examples of suitable R^3 groups are C_{1-3} alkyl (e.g. methyl), but R^3 is preferably a hydrogen atom. R^1 is thus preferably —$(CH_2)_2COOH$.

When R^3 is a hydrogen atom, the compounds are capable of salt formation with bases and the compounds are preferably used in the form of such salts. Examples of suitable salts are alkali metal (e.g. sodium and potassium), alkaline earth metal (e.g. calcium or magnesium), ammonium, substituted ammonium (e.g. tromethamine or dimethylaminoethanol), piperazine, N,N-dimethylpiperazine, morpholine, piperidine and tertiary amino (e.g. triethylamine) salts. Inorganic salts are preferred.

X is preferably a cis —CH=CH— group.

The heterocyclic amino group Y may for example have a 5, 6 or 7-membered ring, e.g.

pyrrolidino, piperidino, morpholino, piperazino, thiamorpholino, 1-dioxothiamorpholino, homomorpholino and hexamethyleneimino. Examples of the optional substituents which may be present in a second nitrogen atom in the ring are methyl, ethyl and benzyl. The carbon atoms of the heterocyclic rings may for example be substituted by methyl or ethyl. Y is preferably piperidino, morpholino, homomorpholino, thiamorpholino or 1-dioxothiamorpholino, and compounds in which Y is a morpholino or piperidino group are particularly preferred.

The amino group Y enables the compounds to form salts with organic acids, e.g. maleates.

R^2 may for example be C_{5-10} alkyl (e.g. pentyl or decyl); C_{3-5} alkenyl (e.g. allyl, optionally substituted by phenyl); or C_{1-5} alkyl (e.g. methyl or propyl) substituted by phenyl [optionally substituted by a C_{1-4} alkyl (e.g. tert butyl), C_{5-7} cycloalkyl (e.g. cyclohexyl), C_{1-3} alkylthio (e.g. methylthio), phenyl (C_{1-3}) alkyl (e.g. benzyl) or thienyl], furanyl or thienyl (optionally substituted by a phenyl group), biphenyl [optionally substituted by C_{1-3} alkyl (e.g. methyl), C_{1-3} alkoxy (e.g. methoxy), halogen (e.g. chlorine) or phenyl], or naphthyl.

R^2 is preferably a phenylalkyl group in which the alkyl portion contains C_{1-3} carbon atoms and the phenyl is substituted with one of the following groups: C_{1-3} alkylthio, thienyl or phenyl optionally substituted by C_{1-3} alkyl, C_{1-3} alkoxy; halogen or phenyl; or is thienylalkyl in which the alkyl portion contains 1—3 carbon atoms and the thienyl group is substituted by a phenyl group; or cinnamyl.

Particularly preferred R^2 groups are phenylalkyl groups in which the alkyl portion is a C_{1-3} alkylene chain and the phenyl group carries a phenyl substituent, preferably in the para-position (which phenyl substituent is optionally substituted by a C_{1-3} alkyl, C_{1-3} alkoxy or halogen, this additional substituent preferably being in the meta or more particularly the para-position); or thienylmethyl group (particularly a 4-thienylmethyl group) substituted by a phenyl group, which substituent is preferably in the 2-position; or cinnamyl.

A particularly preferred group of compounds has the formula (1) in which:

X is cis —CH=CH—,

R^1 is $—CH_2CH_2COOH$,

Y is morpholino or piperidino, and

R^2 is phenyl (C_{1-3}) alkyl in which the phenyl group is substituted by phenyl (which phenyl substituent is optionally substituted by C_{1-3} alkyl, C_{1-3} alkoxy or halogen); phenylthienylmethyl; or cinnamyl,

and the physiologically acceptable salts and solvates (e.g. hydrates) thereof.

Particularly important compounds in this latter group are those in which Y is morpholino and R^2 is 1,1′-biphenylmethyl; 1,1′-biphenylmethyl substituted in the para-position by methyl, methoxy or chloro or in the meta-position by methoxy; 1,1′-biphenylpropyl; 2-phenylthien-4-ylmethyl; or cinnamyl; and those in which Y is piperidino and R^2 is 1,1′-biphenylmethyl or 4′-methoxy-1,1′-biphenylmethyl. Especially important are:

[1α(Z),2β,5α]-(±)-7-[5-[[(1,1′-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxycyclopentyl]-4-heptenoic acid; and

[1R-[1α(Z),2β,5α]]-(—)-7-[5-[[(1,1′-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid; and the hydrates and salts thereof, particularly the calcium, piperidine, piperazine and N,N-dimethylpiperazine salts. The calcium salts are particularly important.

In general, the compounds of formula (1) in which the carbon atom carrying the $—(CH_2)_2XR^1$ group is in the R-configuration (and mixtures containing this isomer) are preferred.

Compounds of formula (1) inhibit blood platlet aggregation and bronchoconstriction. The test for inhibition of platelet aggregation is as described by G. V. Born in Nature *194,* 927—929 (1962) except in that collagen is used instead of ADP as the pro-aggregatory agent. The test for potential inhibition of bronchoconstriction is as described by K. M. Lulich *et al* in British Journal of Pharmacology *58,* 71—79, (1976) except guinea-pig lung is used instead cat lung.

The compounds are thus of interest in the treatment of asthma, and as inhibitors of platelet aggregation and thrombosis for use in renal dialysis and the treatment and prevention of occlusive vascular diseases such as arteriosclerosis, atherosclerosis, peripheral vascular disease, cerebral vascular disease including transient ischaemic attacks, stroke, pulmonary embolism, diabetic retinopathy, post operative thrombosis, angina and myocardial infarction. They may be formulation in conventional manner for use, with one or more pharmaceutical carriers.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets, capsules, powders, solutions, syrups, or suspensions prepared by conventional means with acceptable excipients.

The compounds may be formulated for parenteral administration by bolus injections or continuous infusion. Formulations for injections may be presented in unit dosage form in ampoules, or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution before use with a suitable vehicle, e.g. sterile pyrogen-free water.

For administration by inhalation the compounds are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, or as a cartridge from which the

powdered composition may be inhaled with the aid of a suitable device. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

For use as antithrombotic agents, the compounds are preferably administered orally, for example in amounts of 0.05 to 10 mg/kg body weight, 1 to 4 times daily.

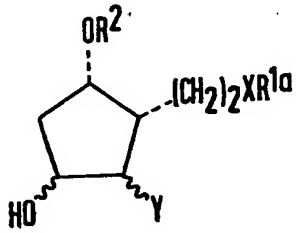
For use in the treatment of asthma, the compounds may also be administered orally in amounts of 0.05 to 10 mg/kg body weight, 1 to 4 times daily; preferably however they are administered by inhalation at doses varying from 0.3 to 30 mg, 1 to 4 times daily. The compounds may be used in combination with other antiasthmatic agents.

The precise dose administered will of course depend on the age and condition of the patent.

Suitable methods for preparing compounds of formula (1) are described below.

In the following discussion, the groups R^1, R^2, R^3, X and Y are as defined above except where otherwise indicated.

(a) Compounds of formula (1) may be prepared by oxidising a corresponding hydroxy compound, e.g. a compound of formula (2)



(2)

(wherein R^{1a} is C_{1-7} alkyl substituted by —$COOR^3$, —CH_2OH or —CHO).

Suitable methods of oxidation include using a Cr^{VI} oxidising reagent in a suitable solvent, e.g. chromic acid in acetone (e.g. Jones reagent, preferably used in the presence of a diatomaceous silica such as Celite) or CrO_3 in pyridine. These reagents are for example used at temperatures of —20° to room temperature.

Other important methods include using an activated sulphur reagent, e.g. (i) N-chlorosuccinimidedimethylsulphide complex in a suitable solvent (e.g. toluene or dichloromethane) at temperatures of for example —25 to 25°, preferably at 0—5°, (ii) a dimethylsulphide (e.g. dimethylsulphoxide) activated by a suitable electrophilic reagent (such as oxalyl chloride, acetyl bromide or thionyl chloride) in a suitable solvent (e.g. toluene or dichloromethane), e.g. at —70 to —20°; dicyclohexylcarbodiimide can also be used as the electrophilic reagent (preferably in the presence of CF_3COOH or its pyridinium salt) at for example —10° to room temperature, using the same solvents, or (iii) pyridine —SO_3 complex in dimethylsulphoxide, preferably at 0° to room temperature.

When R^3 is a hydrogen atom, better yields are sometimes obtained by prior protection of the carboxyl group, for example in the form of a trialkyl (e.g. trimethyl, triethyl or dimethyl (1,1-dimethylethyl))silyl ester.

Cr^{VI} oxidising agents are generally preferred. The choice of oxidation method however will depend on the nature of the starting material of formula (2). Thus when R^{1a} is —CH_2OH or —CHO, a Cr^{VI} oxidising agent will generally be used. When Y is in the α-configuration conditions should be chosen to effect epimerisation, either at the same time or after oxidation.

Any hydroxy or amino group present in the starting material and required in the end product should be suitably protected in this reaction.

(b) Compounds of formula (1) in which R^3 is an alkyl or aralkyl group can be prepared by esterification of the corresponding carboxylic acid in which R^3 is a hydrogen atom, reaction with a diazoalkane being preferred.

Alternatively, the acid may be converted into an activated derivative (e.g. a corresponding mixed anhydride) e.g. by reaction with an alkyl chloroformate (e.g. isobutyl chloroformate) in the presence of a suitable base, e.g. triethylamine or pyridine. The activated derivative can then be reacted with an appropriate alcohol, for example using a solvent such as acetone and temperatures of —10° to room temperature.

(c) Compounds of formula (1) in which R^2 is phenalkyl substituted by amino may be prepared by reduction of the corresponding azide, for example using zinc and sodium dihydrogen phosphate (e.g. in tetrahydrofuran).

(d) Compounds of formula (1) may also be prepared by selective reduction of a corresponding compound of formula (1) in which X is an acetylene group. These intermediates are also novel compounds. Suitable methods of reduction include using hydrogen in the presence of a catalyst, e.g. palladium on a support (e.g. $CaCO_3$ or $BaSO_4$) and poisoned for example by lead or pyridine. Suitable solvents include ethyl acetate or methanol.

(e) Where salts of compounds of formula (1) are desired such salts may be formed by conventional methods, for example by treating acids of formula (1) with appropriate bases. Salts may also be formed with acids.

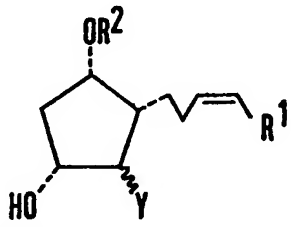
The salts may be formed in conventional manner. For example, amine salts are conveniently prepared by adding the amine to a solution of an acid of formula (1) in a solvent such as ether. Salts of inorganic bases may be prepared by adding the base to a solution of the acid in an aqueous organic solvent. Certain salts may also be prepared by exchange of cation; for example, calcium salts may be prepared by addition of a calcium salt (e.g. the chloride or acetate) to a solution of a salt of a compound of formula (1), e.g. an amine or alkali metal salt.

The principal intermediates required for the reactions described above may be prepared by the following methods.

It will be appreciated that the following reactions will frequently require the use of, or will conveniently be applied to, starting materials having protected functional groups. It is to be understood generally that the references below to specific starting materials are intended to include references to corresponding materials having protected functional groups.

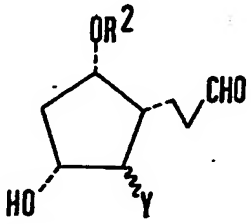
It will also be appreciated that certain of the reactions described below are capable of affecting other groups in the starting material which are desired in the end product, and account must be taken of this when performing multi-stage reactions.

(f) Compounds of formula (3)



(3)

(where R^1 is as defined above for R^1 where R^3 is a hydrogen atom) may be prepared by reacting a compound of formula (4)



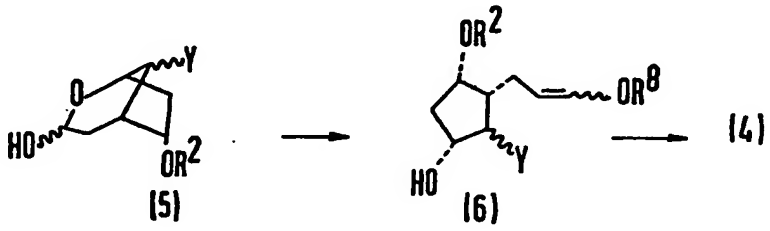
(4)

with an appropriate Wittig reagent, e.g. a phosphorane of formula $R^7_3P{=}CHR^1$ (where R^7 is C_{1-6} alkyl or aryl, e.g. monocyclic aryl such as phenyl) or a salt thereof, e.g. the potassium salt. Suitable reaction solvents include hydrocarbons (e.g. benzene and toluene), ethers (e.g. tetrahydrofuran), dialkylsulphoxides (e.g. dimethylsulphoxide), alcohols and halogenated hydrocarbons. The reaction may be carried out at any suitable temperature from −70° to 50°C, preferably at room temperature.

The reaction is particularly suitable for the preparation of compounds in which R^1 is terminally substituted by —COOH (in salt form). Any hydroxy group present is preferably in a protected state prior to this reaction. Suitable hydroxyl protecting groups are described below. Any $-NH_2$ group present should also be protected, e.g. by t-butoxycarbonyl.

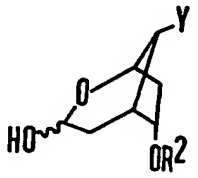
If desired, the configuration of the group X and R^1 and R^2 may then be modified to provide other compounds of formula (2) e.g. by methods (l)—(o) below or (b) or (c) above.

The starting materials of formula (4) may be prepared by the following sequence:



A lactol of formula (5) is treated with an appropriate Wittig reagent (e.g. $R^7_3P{=}CHOR^8$, where R^7 is as defined above and R^8 is C_{1-4} alkyl) to give the vinyl ether (6). The reactions may be performed as described for process (f). The vinyl ether (6) is then hydrolysed to give the aldehyde (4), for example using a dilute acid such as hydrochloric acid. Acetone is a suitable solvent.

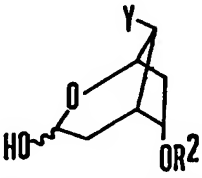
Lactols of the formula (7)



(7)

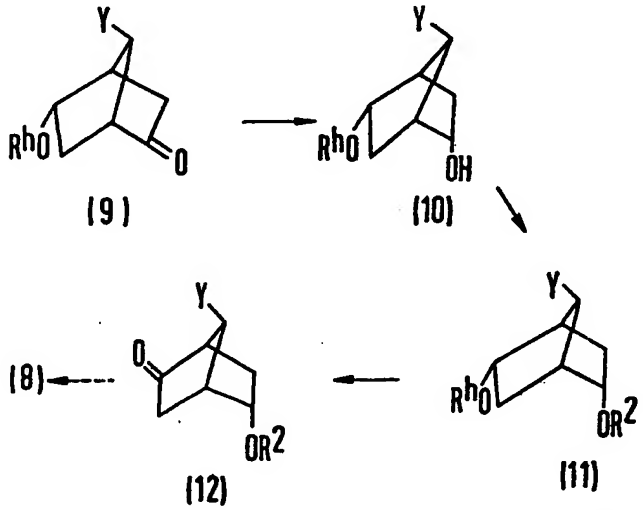
may be prepared by the method described in British Patent Specification 2,028,805A, using starting materials containing the appropriate R^2 group.

Lactols of formula (8)



(8)

required as starting materials may be prepared by the following sequence:



(R^h above represents a hydroxyl protecting group). Thus the norbornanone (9) is first reduced (e.g. with $NaBH_4$) to the alcohol (10) into which the R^2 group is then introduced (e.g. by reaction with R^2L, where L is a leaving group, e.g. halogen or tosylate) to give the compound (11). The protecting group (R^h) is then removed and the hydroxy group oxidised (e.g. as described for process (a)) to give the norbornanone (12). The latter can then be converted into the lactol (8) by Baeyer-Villiger oxidation followed by reduction (e.g. with di-isobutyl aluminium hydride).

(g) Compounds of formula (2) in which the groups Y and OH are both in the β-position may be prepared by reducing the corresponding compound of formula (1), e.g. with lithium tri-sec-butyl borohydride.

(h) Compounds of formula (2) in which R^{1a} contains —CH_2OH may be prepared by reducing the corresponding acid or ester of formula (2) or (1), e.g. with $LiAlH_4$.

(j) Compounds of formula (2) in which R^{1a} contains —CHO may be prepared in the same manner as generally described for process (f) by reacting a compound of formula (4) with a phosphorane of formula $R^7_3P{=}CHR^{1a}$ in which R^{1a} is C_{1-7} alkyl substituted by a protected formyl group (e.g. acetal). Removal of the protecting group then gives the required formyl intermediate.

(k) Compounds of formula (2) in which Y is in the α-configuration and the ring hydroxy group is in the β-configuration may be prepared by epimerising the corresponding compound in which the ring hydroxy group is in the α-position. This may for example be effected with triphenylphosphine in the presence of an acid (e.g. formic or benzoic acid) and $(C_2H_5OOC \cdot N)_2$ at a low temperature. Tetrahydrofuran is a suitable solvent.

(l) The acetylenes required as starting materials for process (d) may be prepared by first reacting a compound of formula (7) with a Wittig reagent ($R^7_3P{=}CBrR^1$), as described above for process (f). The product is then dehydrobrominated to form the side chain acetylene group, and the ring hydroxy group then oxidised, as described for process (a).

(m) Compounds of formula (2) in which X is trans —CH=CH— may be prepared by isomerising

the corresponding cis compound. The isomerisation may for example be effected by treatment with, for example, p-toluene sulphinic acid in dioxan (e.g. at reflux) or azobisisobutyronitrile and thiophenol, using for example a hydrocarbon solvent (e.g. benzene) and any suitable temperature up to reflux.

(n) Compounds of formula (2) in which R^2 is phenalkyl substituted by $—CH_2N(CH_3)_2$ may be prepared by treatment of the corresponding formyl compound with dimethylamine in the presence of a reducing agent, e.g. sodium cyano borohydride. The starting materials for this reaction may be made by the general method (f).

(o) Compounds of formula (2) in which R^2 is phenalkyl substituted by $—CONH_2$ or $—CSNH_2$ and R^3 is hydrogen may be prepared from the corresponding cyano compound by hydrolysis or hydrosulphidation, e.g. with sulphur in the presence of a reducing agent.

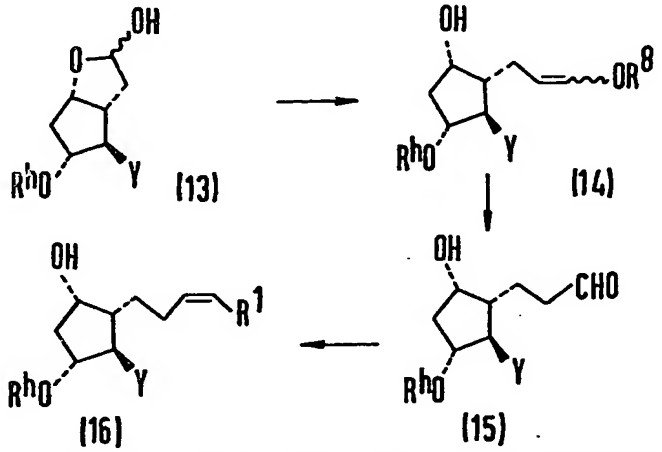
(p) Compounds of formula (2) in which R^2 is phenalkyl substituted by alkylsulphinyl or alkylsulphonyl may be prepared by oxidation of the corresponding alkylthio compound with a peracid, for example peracetic acid at room temperature.

(q) Compounds of formula (3) in which $—OR^2$ is an ether group and Y is in the β-configuration may be prepared by etherification of the corresponding hydroxy compound in which R^2 is a hydrogen atom. The reaction may for example be performed with an appropriate reagent R^2L (L is as defined above), for example by reaction at room temperature in the presence of a suitable base (e.g. sodium hydride) in a suitable solvent (e.g. dimethylformamide).

(r) Compounds of formula (3) in which R^2 is an alkanoyl group and Y is in the β-configuration may be prepared by acylation of the corresponding hydroxy compound, for example with the appropriate alkanoic acid or an anhydride or halide thereof.

Any other hydroxy group present in the starting material used in process (q) or (r) should be protected in this reaction, as should the —COOH group in compounds in which R^3 is a hydrogen atom.

Suitable starting materials of formula (16) for processes (q) and (r) above may be prepared by the following sequence:



A lactol of formula (13), in which $—OR^h$ is a protected hydroxy group is first treated with a Wittig reagent to give the vinyl ether (14), which is then converted into the aldehyde (15) by treatment with mercuric acetate. These steps are performed in the same general way as for the preparation of compounds of formula (4). The compound of formula (16) may then be formed from the aldehyde (15) by method of process (f).

The preparation of the lactols (13) is described in British Patent Specification 2,028,805A.

As an alternative to the formation of the ether group by process (q), it may be formed at an earlier stage, by etherification of the compound of formula (14).

(s) Compounds of formula (2) may also be prepared by modifying the corresponding compound in which Y is $—NH_2$.

This reaction may be performed by treating the starting material with a compound of the formula ZR^9Z, where Z is a readily displaceable group (such as halo, e.g. iodo, or hydrocarbylsulphonyloxy, e.g. p-toluenesulphonyloxy) and R^9 is the appropriate divalent group (e.g. $—(CH_2)_2S(CH_2)_2—$). The reaction may be carried out in a solvent such as acetonitrile or methanol at reflux, in the presence of a suitable base, e.g. potassium carbonate or sodium bicarbonate.

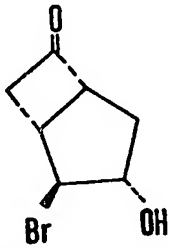
The amines required as starting materials for process (s) may be prepared by reduction of the corresponding azide, for example as described for process (c).

The azide starting materials may be prepared by methods analogous to those for preparing the compounds of formula (3), using reagents in which Y is an azido group. In particular, the preparations of lactols of formula (7) in which Y is azido is described in British Patent Specification 2,028,805A.

If desired, modification of the group R^1 or the configuration of the double bond may be effected before the formation of the group Y by process (s). The amino group may need to be protected in such transformations.

In the preparation of the intermediates the ring hydroxy group will often be protected and the liberation of this (or any other hydroxy group present) will frequently be the last step in the preparation. Conventional methods of protection may be used, protection in the form of dimethyl-1,1-dimethylethyl-silyloxy or tetrahydropyranyloxy groups being preferred. These groups may be removed by acid hydrolysis. Hydroxy groups may also be protected in the form of alkanoyloxy groups having up to 7 carbon atoms, e.g. acetoxy. These groups may be removed by alkaline hydrolysis.

When a specific enantiomer of formula (1) is required, intermediates having the required stereochemical configuration should be used in the above processes. For example, enantiomeric bromohydrin (17)



(17)

can be prepared by the method described by Newton et al in J.C.S. Chem. Comm., 1979, 908. This can then be converted into a compound of formula (I) in which the carbon atom carrying the $-(CH_2)_2XR^1$ group is in the (R)-configuration, via the appropriate enantiomer of the lactol (7), using the methods described above.

The following examples illustrate the invention. "Jones reagent" is a solution of chromic acid and sulphuric acid in water. A 2.67M solution contains CrO_3 (26.7 g) and concentrated H_2SO_4 (23 ml) made up to 100 ml with water.

Temperatures are in °C. The following abbreviations are used:

TLC—thin layer chromatography using SiO_2; PE—petroleum ether (boiling at 40—60° unless otherwise stated); DIBAL—diisobutylaluminium hydride; THF—tetrahydrofuran; DMF—dimethylformamide; ER—ether; EA—ethyl acetate; DMSO—dimethylsulphoxide. Chromatography was carried out using silica gel unless otherwise stated. 'Dried' refers to drying with $MgSO_4$. 'Hyflo' is a filtration aid.

Intermediate 1

(*endo, anti*)-(±)-5-hydroxy-7-(4-morpholinyl)bicyclo[2.2.1]heptan-2-one

A mixture of (*endo,anti*)-5-acetyl-7-(4-morpholinyl)bicyclo[2.2.1]heptan-2-one (164 g) and 5N NaOH solution (750 ml) was stirred for 3 h and then extracted with CH_2Cl_2 (4×500 ml). The dried organic layers were evaporated *in vacuo* to give a semi-solid. Trituration with ER (500 ml) gave the *title compound* (83 g) as prisms, m.p. 119—121°.

Intermediate 2

a) (*endo,anti*)-(±)-5-[[(1,1'-biphenyl-4-yl]methoxy]-7-(4-morpholinyl)bicyclo[2.2.1]heptan-2-one

To a solution of Intermediate 1 (10.5 g), 1-(bromomethyl)-1,1'-biphenyl (13.6 g) and benzyltriethyl ammonium chloride (1.14 g) in CH_2Cl_2 (200 ml) was added 17N NaOH (100 ml) and the mixture stirred vigorously for 18 h. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×100 ml). The combined organic layers were washed with water (200 ml), dried and evaporated *in vacuo*. The residue was crystallised from Iso-propyl acetate to give the *title compound* (15 g) as prisms, m.p. 149.5—151.5°. The following compounds were prepared by a similar procedure.

b) (*endo,anti*)-(±)-5-[4-methoxy(phenylmethoxy)]-7-(4-morpholinyl)bicyclo[2.2.1]heptan-2-one

m.p. 109—111°, from Intermediate 1 and p-methoxybmzyl bromide. Purification by chromatography using 3:1 ER-PE through to 5:1 ER-methanol as eluent.

(±)-4-[(*endo,endo,anti*)-2-[[(1,1'-biphenyl)-4-yl]methoxy]-5-[(tetrahydro-2H-pyran-2-yl)oxy]bicyclo[2.2.1]heptan-7-yl]morpholine

m.p. 109—110° from Intermediate 27. Purification by chromatography using 7:3 ER-PE as eluent.

d) (*endo,anti*)-(±)-5-[[(1,1'-biphenyl)-4-yl]methoxy]-7-(1-piperidinyl)bicyclo[2.2.1]heptan-2-one

m.p. 89—91° form Intermediate 57. Purification by chromatography using 3:2 PE-ER as eluent.

Intermediate 3

a) (*endo,anti*)-(±)-6-[[(1,1'-biphenyl)-4-yl]methoxy]-8-(4-morpholinyl)-2-oxabicyclo[3.2.1]octan-3-one

38% Peracetic acid in acetic acid (20 ml) was added dropwise over 10 min to a stirred solution of Intermediate 2a (12.5 g) in CH_2Cl_2 (60 ml) maintained at 12—15°. Stirring was continued at 15—20°

for 24 h, the mixture then cooled to 5° and treated with a solution of Na_2SO_3 (25.1 g) in water (125 ml) whilst maintaining the temperature below 20°. Isopropyl acetate (90 ml) was added and the aqueous phase was separated. The organic phase was extracted with 1N NaOH (60 ml) and water (2×60 ml), then dried and reduced in volume to about 35 ml. On cooling to 20° the *title compound* crystallised and was collected and dried (6.25 g), m.p. 137—139°.

The following compounds were prepared by a similar procedure:

b) (*endo,anti*)-(±)-6-[4-methoxy(phenylmethoxy]-8-(4-morpholinyl)-2-oxabicyclo[3.2.1]octan-3-one
m.p. 158—160°, from Intermediate 2b. Purification from CH_2Cl_2—PE.

c) (*endo,anti*)-(±)-6-[[(1,1′-biphenyl)-4-yl]methoxy]-8-(1-piperidinyl)-2-oxabicyclo[3.2.1]octan-3-one
m.p. 88—90° from Intermediate 2d.

d) (*endo,anti*)-(±)-6-decyloxy-8-(4-morpholinyl)-2-oxabicyclo[3.2.1]octan-3-one
m.p. 59—61°, from Intermediate 80. Purification from PE.

Intermediate 4
a) (1α,2β,3α,5α)-(±)-5-[[(1,1′-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentane Acetaldehyde

DIBAL in hexane (1.4 M; 6.9 ml) was added dropwise to a solution of Intermediate 3a) (1.9 g) in dry CH_2Cl_2 (30 ml) under nitrogen at —70°. Stirring was continued for 2 h at —70° when methanol (50 ml) was cautiously added and the mixture then allowed to come to ambient temperature and stirred for a further 3 h. The mixture was filtered through hyflo and the filtrate evaporated *in vacuo*. The residue was taken up into CH_2Cl_2 (50 ml), dried, filtered and concentrated to give the *title compound* as a glass (1.8 g).

I.R. ($CHBr_3$) 3580, 1718 cm^{-1}.

The following compounds were prepared by a similar procedure:

b) (1α,2β,3α,5α)-(±)-3-hydroxy-5-[4-methoxy(phenylmethoxy)]-2-(4-morpholinyl)cyclopentane Acetaldehyde
from Intermediate 3b. Purification by chromatography using 98:2 $CHCl_3$-methanol as eluent.
TLC 95:5 $CHCl_3$-methanol Rf 0.8.

c) (1α,2α,3α,5α)-(±)-5-[[(1,1′-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentane Acetaldehyde
m.p. 136—138° from Intermediate 30.

d) (3aα,4α,5β,6aα)-(±)-hexahydro-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-(4-thiomorpholinyl)-2H-cyclopenta(b) furan-2-ol
from Intermediate 55a.
TLC 9:1 Benzene-methanol Rf 0.25.

e) (1α,2β,3α,5α)-(±)-5-[[(1,1′-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentane Acetaldehyde
from Intermediate 3c. TLC 85:15 ER-methanol Rf 0.38.

f) (3aα,4α,5β,6aα)-(±)-hexahydro-4-(hexahydro-1,4-oxazepin-4-yl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-cyclopenta(b)furan-2-ol
from Intermediate 55b. TLC 9:1 ER-methanol Rf 0.31.

g) (1α,2β,3α,5α)-(±)-5-decyloxy-3-hydroxy-2-(4-morpholinyl)cyclopentane Acetaldehyde
from Intermediate 3d. TLC (SiO_2) EA R_f 0.21.

Intermediate 5
a) (1α,2β,3α,4α)-(±)-4-[[(1,1′-biphenyl)-4-yl]methoxy]-3-(3-methoxy-2-propenyl)-2-(4-morpholinyl)cyclopentanol

To a cold (0°) stirred solution of potassium *tert*-butoxide (1.55 g) in dry THF (40 ml) under nitrogen, was added portionwise (methoxymethyl)triphenyl phosphonium chloride (4.72 g). The resulting suspension was stirred for 25 min whereupon a solution of Intermediate 4a) (1.82 g) in dry THF (15 ml) was added dropwise. Stirring was continued at room temperature for 1.5 h. The reaction mixture was poured into brine, the pH adjusted to 6.5, and the mixture extracted with EA. The dried extracts were evaporated to leave a viscous oil. This crude material was flash chromatographed on silica. Eluting with 95:5 EA-methanol and recycling of the impure fractions gave the *title compound* as an oil (1.29 g). IR ($CHBr_3$) 3950 (br), 3540, 1668 cm^{-1}.

The following compounds were prepared in a similar manner.

b) (1α,2α,3β,4α)-(±)-2-(3-methoxy-2-propenyl)-4-[(tetrahydro-2H-pyran-2-yl)oxy]-3-(4-thiomorpholinyl)cyclopentanol
from Intermediate 4d. Purification by chromatography using ether as eluent. TLC ER Rf 0.28.

c) (1α,2α,3β,4α)-(±)-2-(3-methoxy-2-propenyl)-3-(1-piperidinyl)-4-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentanol
from (3aα,4α,5β,6aα)-(±)-hexahydro-4-(1-piperidinyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-cyclopenta(b)furan-2-ol. TLC 4:1 EA-methanol Rf 0.22.

Intermediate 6
(1α,2β,3α,5α)-(±)-5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentane Propanal, Hydrochloride

Intermediate 5a (1.835 g) was dissolved in 1:1 acetone/0.5N H_2SO_4 (65 ml) and was left standing overnight at room temperature. The acetone was evaporated and the residue treated with 8% $NaHCO_3$ solution and extracted with EA. The dried extracts were evaporated to give a foam (1.73 g) which was dissolved in ether and treated with ethereal hydrogen chloride. The *title compound* was filtered off and dried, m.p. 169—172°.

Intermediate 7
a) (1α,2α,3β,4α)-(±)-2-(3-methoxy-2-propenyl)-3-(4-morpholinyl)-4-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentanol, Acetate (Ester)

To a cold (0°) stirred solution of potassium *tert*-butoxide (2.15 g) in dry THF (40 ml) under nitrogen, was added portionwise (methoxymethyl)triphenyl phosphonium chloride (6.57 g). The suspension was stirred for 15 min, whereupon a solution of (3aα,4α,5β,6aα)-hexahydro-4-(4-morpholinyl)-5-(tetrahydro-2H-pyran-2-yl)oxy-2H-cyclopenta(b)furan-2-ol (2 g) in dry THF (30 ml) was added dropwise. Stirring was continued at room temperature for 1 h, when methanol (30 ml) was added followed by evaporation of the mixture to dryness. The residue was treated with acetic anhydride (8 ml) and pyridine (10 ml) and left for 40 h. Evaporation *in vacuo* gave a residue which was treated with 8% $NaHCO_3$ solution (50 ml) and extracted with CH_2Cl_2 (3x20 ml). The combined extracts were washed with brine (2x15 ml), dried and concentrated. Purification of the residue, initially by chromatography using 4:1 ER-methanol as eluent, and then by trituration with PE gave the *title compound* as an oil (13.23 g). IR (Neat) 1735, 1655 cm^{-1}.

The following compounds were prepared in a similar manner.

b) (1α,2α,3β,4α)-(±)-2-(3-methoxy-2-propenyl)-4-[(tetrahydro-2H-pyran-2-yl)oxy]-3-(4-thiomorpholinyl)cyclopentanol, Acetate (Ester), S-dioxide
m.p. 131—134° from Intermediate 63. Purification initially by chromatography using 1:1 EA-PE as eluent followed by crystallisation from isopropanol-ER-isopentane.

c) (1α,2α,3β,4α)-(±)-3-(hexahydro-1,4-oxazepin-4-yl)-2-(3-methoxy-2-propenyl)-4-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentanol, Acetate (Ester)
from Intermediate 4f. Purification by chromatography using 95:5 ER-methanol as eluent. TLC 19:1 ER-methanol Rf 0.65.

Intermediate 8
(1α,2α,3β,4α)-(±)-2-(3-methoxy-2-propenyl)-3-(4-morpholinyl)-4-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentanol

A solution of Intermediate 7a (0.3 g) in 0.5N NaOH (10 ml) was left to stand for 10 min, then extracted with ER (3x20 ml). The combined extracts were dried, filtered and evaporated to give the *title compound* as an oil (0.25 g). IR (Neat) 3450, 1655 cm^{-1}.

Intermediate 9
a) (1α,2β,3β,5β)-(±)-4-[3-(2-naphthalenylmethoxy)-2-(3-methoxy-2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine

NaH (0.48 g, 80% dispersion in oil) was added to a solution of Intermediate 8 (2.2 g) and bromomethyl)naphthalene (3.56 g) in dry DMF (8 ml) at 0°C. After stirring for 7 H, the suspension was poured into saturated NH_4Cl solution (75 ml) and extracted into ER (3x50 ml). The combined extracts were dried and concentrated, and the residue chromatographed on silica using ER as eluent to give the *title compound* as an oil (2.1 g). IR (Neat) 1716, 1655 cm^{-1}.

The following compounds were prepared by a similar procedure:

b) (1α,2β,3β,5β)-(±)-4-[2-(3-methoxy-2-propenyl)-3-[4-(1,1-dimethylethyl)phenylmethoxy]5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine
from Intermediate 8 and 4-(1,1-dimethylethyl)phenylmethyl bromide. Purification by chromatography using ER as eluent. IR (Neat) 1650, 1120 cm^{-1}.

c) (1α,2β,3β,5β)-(±)-4-[3-(4-cyclohexylphenylmethoxy)-2-(3-methoxy-2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine
from Intermediate 8 and 4-cyclohexylphenylmethyl iodide. Purification by chromatography using ER as eluent.

d) (1α,2β,3β,5β)-(±)-4-[2-(3-methoxy-2-propenyl)-3-(pentyloxy)-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine
from Intermediate 8 and n-pentyl-tosylate. Purification by chromatography using EA as eluent.

e) (1α,2β,3β,5β)-(±)-4-[2-(3-methoxy-2-propenyl)-3-[4-(phenylmethyl)phenylmethoxy]-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine
from Intermediate 8 and 1-(bromomethyl)-4-(phenylmethyl)benzene. Purification by chromatography using ER as eluent.

f) (1α,2β,3β,5β)-(±)-4-[3-[[4'-chloro(1,1'-biphenyl)-4-yl]methoxy]-2-(3-methoxy-2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine
from Intermediates 8 and 68. IR (Neat) 1650, 1120 cm^{-1}.

g) (1α,2β,3β,5β)-(±)-4-[2-(3-methoxy-2-propenyl)-3-(2-propenyloxy)-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine
from Intermediate 8 and allyl bromide.

h) (1α,2β,3β,5β)-(±)-4-[2-(3-methoxy- 2-propenyl)-3-[4-methylthio)phenylmethoxy)]-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine
from Intermediate 8 and 1-(bromomethyl)-4-(methylthio)benzene. Purification by chromatography using ER as eluent. IR (Neat) 1650, 1120 cm^{-1}.

i) (1α,2β,3β,5β)-(±)-4-[2-(3-methoxy-2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-3-[(4-thien-2-yl)phenylmethoxy]cyclopentyl]morpholine
from Intermediates 8 and 24a. Purification by chromatography using ER as eluent.

j) (1α,2β,3β,5β)-(±)-4-[2-(3-methoxy-2-propenyl)-3-[[(1,1':4',1"-terphenyl)-4-yl]methoxy]-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine
from Intermediates 8 and 24b. Purification by chromatography using ER as eluent. TLC ER Rf 0.18.

k) (1α,2β,3β,5β)-(±)-4-[2-(3-methoxy-2-propenyl)-3-(4-phenylthien-2-yl)methoxy]-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine
from Intermediates 8 and 65. Purification by chromatography using EA as eluent.

l) [1α,2β,3β(E),5β]-(±)-4- [2-(3-methoxy-2-propenyl)-3-[(3-phenyl-2-propenyl)oxy]-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine
from Intermedaite 8 and cinnamyl bromide. Purification by chromatography using ether as eluent.

m) (1α,2β,3β,5β)-(±)-4-[3-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(3-methoxy-2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]thiomorpholine
from Intermediate 5b and 1-(bromomethyl)-1,1'-biphenyl. Purification by chromatography using 3:2 ER-PE. TLC ER Rf 0.42.

n) (1α,2β,3β,5β)-(±)-4-[3-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(3-methoxy-2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]thiomorpholine, S-dioxide
from Intermediate 59a and 4-(bromomethyl)-4'-methoxy(1,1'-biphenyl). Purification by chromatography using CH_2Cl_2 followed by ER as eluents. TLC ER Rf 0.41.

o) (1α,2β,3β,5β)-(±)-4-[2-(3-methoxy-2-propenyl)-3-[[4'-methyl(1,1'-biphenyl)-4-yl]methoxy]-5-(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]thiomorpholine, S-dioxide
from Intermediates 59a and 66. Purification by chromatography using CH_2Cl_2 followed by 4:1 ER-PE as eluent.

p) (1α,2β,3β,5β)-(±)-4-[2-(3-methoxy-2-propenyl)-3-[4-(phenylmethyl)phenylmethoxy]-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]thiomorpholine, S-dioxide
from Intermediate 59a) and 1-(bromomethyl)-4-(phenylmethyl)benzene. Purification by chromatography using CH_2Cl_2 followed by ER as eluents. TLC EA Rf 0.5.

q) (1α,2β,3β,5β)-(±)-4-[3-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(3-methoxy-2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]thiomorpholine, S-dioxide
from Intermediate 59a and 1-(bromomethyl)-1,1'-biphenyl. TLC 95:5 ER-methanol Rf 0.7.

r) (1α,2β,3β,5β)-(±)-4-[3-[(1,1'-biphenyl)-4-yl]methoxy]-2-(3-methoxy-2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]hexahydro-1,4-oxazepin
from Intermediate 59b. TLC 97:3 ER-methanol Rf 0.68.

s) (1α,2β,3β,5β)-(±)-1-[3-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(3-methoxy-2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]piperidine
from Intermediate 5c. Purification by chromatography using 98:2 CH_2Cl_2-methanol as eluent.

t) (1α,2β,3β,5β)-(±)-4-[3-[[(1,1'-biphenyl)-4-yl]propoxy]-2-(3-methoxy-2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine
from Intermediates 8 and 60. Purification by chromatography using EA as eluent.

u) (1α,2β,3β,5β)-(±)-4-[3-[[3'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(3-methoxy-2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine
from Intermediates 8 and 24c. Purification by chromatography using EA as eluent.

v) (1α,2β,3β,5β)-(±)-4-[3-[[4'-methoxy(1,1'-biphenyl)-3-yl]methoxy]-2-(3-methoxy-2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine
from Intermediate 8 and 3-(bromomethyl)-4'-methoxy(1,1'-biphenyl). Purification by chromatography using EA as eluent.

Intermediate 10

a) (1α,2β,3α,5α)-(±)-3-hydroxy-2-(4-morpholinyl)-5-(2-naphthalenylmethoxy)cyclopentanepropanal

A solution of Intermediate 9a (2.1 g) in acetone (10 ml) containing 2N hydrochloric acid (5 ml) was allowed to stand at room temperature for 1 h. After evaporation *in vacuo* the residue was neutralised with 8% $NaHCO_3$ solution and extracted with CH_2Cl_2 (3x30 ml). The combined extracts were dried, filtered and concentrated to afford the *title compound* as a viscous oil (1.7 g). IR (Neat) 3420, 1720 cm^{-1}.

The following compounds were prepared by a similar procedure:

b) (1α,2β,3α,5α)-(±)-3-hydroxy-5-[4-(1,1-dimethylethyl)phenylmethoxy]-2-(4-morpholinyl)cyclopentanepropanal
from Intermediate 9b. TLC 4:1 ER-methanol Rf 0.52.

c) (1α,2β,3α,5α)-(±)-5-(4-cyclohexylphenylmethoxy)-3-hydroxy-2-(4-morpholinyl)cyclopentanepropanal
from Intermediate 9c. TLC 17:3 ER-methanol Rf 0.28.

d) (1α,2β,3α,5α)-(±)-3-hydroxy-2-(4-morpholinyl)-5-(pentyloxy)cyclopentanepropanal
from Intermediate 9d. TLC 95:5 EA-methanol Rf 0.08.

e) (1α,2β,3α,5α)-(±)-3-hydroxy-2-(4-morpholinyl)-5-[4-(phenylmethyl)phenylmethoxy]cyclopentanepropanal
from Intermediate 9e. Purification by chromatography using 9:1 ER-methanol as eluent.

f) (1α,2β,3α,5α)-(±)-5-[[4'-chloro(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentanepropanal
from Intermediate 9f. Purification by chromatography using $CHCl_3$ through to 98:2 $CHCl_3$-methanol as eluent.

g) (1α,2β,3α,5α)-(±)-3-hydroxy-2-(4-morpholinyl)-5-(2-propenyloxy)cyclopentanepropanal
from Intermediate 9g. Purification by chromatography using 4:1 ER-methanol as eluent.

h) (1α,2β,3α,5α)-(±)-3-hydroxy-5-[4-methylthio(phenylmethoxy)]-2-(4-morpholinyl)cyclopentanepropanal
from Intermediate 9h. Purification by chromatography using 85:15 ER-methanol as eluent. TLC 85:15 ER-methanol Rf 0.28.

i) (1α,2β,3α,5α)-(±)-3-hydroxy-2-(4-morpholinyl)-5-[(4-thien-2-yl)phenylmethoxy]cyclopentanepropanal
from Intermediate 9i. Purification by chromatography using $CHCl_3$ through to 98:2 $CHCl_3$-methanol as eluent. TLC 95:5 $CHCl_3$-methanol Rf 0.3.

j) (1α,2β,3α,5α)-(±)-3-hydroxy-2-(4-morpholinyl)-4-[[(1,1':4',1''-terphenyl)-4-yl]methoxy]cyclopentanepropanal
m.p. 151—153° from Intermediate 9j.

k) (1α,2β,3α,5α)-(±)-3-hydroxy-2-(4-morpholinyl)-5-[(4-phenylthien-2-yl)methoxy]cyclopentanepropanal
from Intermediate 9k. Purification by chromatography using 9:1 ER-methanol as eluent. IR ($CHBr_3$) 3580—3540, 2720, 1718 cm^{-1}.

l) [1α,2β,3α,5α(E)]-(±)-3-hydroxy-2-(4-morpholinyl)-5-[(3-phenyl-2-propenyl)oxy]cyclopentanepropanal
from Intermediate 9 l. IR ($CHBr_3$) 3580, 3560, 1720 cm^{-1}.

m) (1α,2β,3α,5α)-(±)-5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-thiomorpholinyl)cyclopentanepropanal
m.p. 109—110° from Intermediate 9m. Purification by chromatography using ER as eluent.

n) (1α,2β,3α,5α)-(±)-3-hydroxy-5-[[(4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(4-thiomorpholinyl)cyclopentanepropanal, S-dioxide
from Intermediate 9n. IR ($CHBr_3$) 3580, 2720, 1720 cm^{-1}.

o) (1α,2β,3α,5α)-(±)-3-hydroxy-5-[[4'-methyl(1,1'-biphenyl)-4-yl]methoxy]-2-(4-thiomorpholinyl)cyclopentanepropanal, S-dioxide
from Intermediate 9o. IR ($CHBr_3$) 3580, 2725, 1720 cm^{-1}.

p) (1α,2β,3α,5α)-(±)-3-hydroxy-5-[4-(phenylmethyl)phenylmethoxy]-2-(4-thiomorpholinyl)cyclopentanepropanal, S-dioxide
from Intermediate 9p. IR ($CHBr_3$) 3580, 2720, 1720 cm^{-1}.

q) (1α,2β,3α,5α)-(±)-5- [[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-thiomorpholinyl)cyclopentanepropanal, S-dioxide
m.p. 152.5—154° (dec.) from Intermediate 9q.

r) (1α,2β,3α,5α)-(±)-5- [[1,1'-biphenyl)-4-yl]methoxy]-2-hexahydro-1,4-oxazepin-4-yl)-3-hydroxycyclopentane propanal
from Intermediate 9r. IR ($CHBr_3$) 3580, 2730, 1720 cm^{-1}.

s) (1α,2β,3α,5α)-(±)-3-hydroxy-5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(1-piperidinyl)cyclopentanepropanal
from Intermediate 9s. IR ($CHBr_3$) 3520, 2730, 1720 cm^{-1}.

t) (1α,2β,3α,5α)-(±)-5-[3-[1,1'-biphenyl)-4-yl]propoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentanepropanal
from Intermediate 9t. IR ($CHBr_3$) 3580, 2730, 1723 cm^{-1}.

u) (1α,2β,3α,5α)-(±)-[3-hydroxy-5-[[3'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)]cyclopentanepropanal
from Intermediate 9u. IR ($CHBr_3$) 3580, 2720, 1720 cm^{-1}.

v) (1α,2β,3α,5α)-(±)-[3-hydroxy-5-[[4'-methoxy(1,1'-biphenyl)-3-yl]methoxy]-2-(4-morpholinyl)]cyclopentanepropanal
from Intermediate 9v. IR ($CHBr_3$) 3560, 2720, 1720 cm^{-1}.

Intermediate 11
(1α,2β,3α,5α)-(±)-3-hydroxy-5-[4-methoxy(phenylmethoxy)]-2-(4-morpholinyl)cyclopentanepropanal

Prepared as an oil from Intermediate 4b according to the methods described for Intermediates 5 and 6. IR (Neat) 3380 (br.), 2720, 1720, 118 cm^{-1}.

Intermediate 12
a) [1α(Z),2β,3α,5α]-(±)-7-[5-[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid

To an intimate mixture of potassium *tert*-butoxide (1.29 g) and (3-carboxypropyl)triphenylphosphonium bromide (2.41 g) under nitrogen was added dry THF (50 ml). The suspension formed was stirred for 30 min whereupon a solution of the free base of Intermediate 6 (1.18 g) in dry THF (50 ml) was added dropwise. Stirring was maintained for 1.5 h whereupon water was added and all organic solvents were evaporated. The pH of the remaining suspension was adjusted to 10 with 2N NaOH solution and the suspension was then extracted with EA to remove phosphorus contaminants. The pH was then adjusted to about 6.5 with phosphate buffer and the product extracted from the suspension with EA. The dried extracts were filtered and concentrated to give the *title compound* as a foam (0.93 g). IR ($CHBr_3$) 3460, 1710 cm^{-1}.

Hydrochloride Salt

To a solution of Intermediate 12a (0.25 g) in EA (5 ml) was added ethereal hydrogen chloride until no more cloudiness was produced. The solvents were decanted and the resulting oil repeatedly washed with dry ER to give a powder (0.13 g), m.p. 125.5—126.5°.

Methanesulphonate Salt

To a solution of Intermediate 12a (0.044 g) in EA (2 ml) was added methanesulphonic acid (0.01 g) at 20° and the mixture stirred for 1 h. The solid was filtered off, washed with EA and dried. Recrystallisation from ethanol gave material of m.p. 171—174°.

The following compounds were prepared by a similar procedure:

b) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-2-(4-morpholinyl)-5-(2-naphthalenylmethoxy)cyclopentyl]-4-heptenoic Acid
from Intermediate 10a. Purification by chromatography using 85:15 ER-methanol as eluent. IR (Neat) 3450—2300 (br.), 1715 cm^{-1}.

c) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-5-[4-methoxy(phenylmethoxy)]-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid
from Intermediate 11. Purification by chromatography using 95:5 $CHCl_3$-methanol as eluent. IR ($CHBr_3$) 3580, 3500, 1720, 1710 cm^{-1}.

d) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-5-[4-(1,1-dimethylethyl)phenylmethoxy]-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid
from Intermediate 10b. Purification by chromatography using 9:1 ER-methanol as eluent. IR ($CHBr_3$) 3500, 1740, 1710 cm^{-1}.

e) [1α(Z),2β,3α,5α]-(±)-7-[5-(4-cyclohexylphenylmethoxy)-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid
from Intermediate 10c. IR ($CHBr_3$) 3500, 1720, 1708 cm^{-1}.

f) [1α(Z), 2β,3α,5α]-(±)-7-[3-hydroxy-2-(4-morpholinyl)-5-(pentyloxy)cyclopentyl]-4-heptenoic Acid
from Intermediate 10d. Purification by chromatography using acetone as eluent.

g) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-2-(4-morpholinyl)-5-[4-(phenylmethyl)phenylmethoxy]cyclopentyl]-4-heptenoic Acid
from Intermediate 10e. Purification by chromatography using 4:1 ER-methanol as eluent.

h) [1α(Z),2β,3α,5α]-(±)-7-[5-[[4′-chloro(1,1′-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid
from Intermediate 10f. Purification by chromatography using $CHCl_3$ through to 96:4 $CHCl_3$-methanol as eluent. IR ($CHBr_3$) 3500, 1710 cm^{-1}.

i) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-2-(4-morpholinyl)-5-(2-propenyloxy)cyclopentyl]-4-heptenoic Acid
from Intermediate 10g. Purification by chromatography using 9:1 ER-methanol as eluent. IR ($CHBr_3$) 3500, 1740—1710 (br.) cm^{-1}.

j) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-5-[4-methylthio(phenylmethoxy)]-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid
from Intermediate 10h. Purification by chromatography using 9:1 ER-methanol as eluent. IR ($CHBr_3$) 3600—3400 (br.), 1730 (sh.), 1710 cm^{-1}.

k) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-2-(4-morpholinyl)-5-[(4-thien-2-yl)phenylmethoxy]cyclopentyl]-4-heptenoic Acid
from Intermediate 10i. Purification by chromatography using $CHCl_3$ through to 94:6 $CHCl_3$-methanol as eluent. IR ($CHBr_3$) 3500, 1738, 1710 cm^{-1}.

l) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-2-(4-morpholinyl)-5-[[(1,1′:4,1″-terphenyl)-4-yl]methoxy]cyclopentyl]-4-heptenoic Acid
from Intermediate 10j. IR ($CHBr_3$) 3500, 1720 cm^{-1}.

m) [1α(Z),2β,3α,5α]-(±)-9-[5-[[(1,1′-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-6-nonenoic Acid
from Intermediate 6 and (5-carboxypentyl)triphenylphosphonium bromide. IR ($CHBr_3$), 3510, 1730 (Sh.), 1710 cm^{-1}.

n) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-2-(4-morpholinyl)-5-[(4-phenylthien-2-yl)methoxy]cyclopentyl]-4-heptenoic Acid
from Intermediate 10k.

o) [1α(Z),2β,3α,5α(E)]-(±)-7-[3-hydroxy-2-(4-morpholinyl)-5-[(3-phenyl-2-propenyl)oxy]cyclopentyl]-4-heptenoic Acid
from Intermediate 10l. Purification by chromatography using 9:1 ether-methanol as eluent. IR ($CHBr_3$) 3500, 1720 cm^{-1}.

p) [1α(Z),2β,3α,5α]-(±)-7-[5-[[1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-thiomorpholinyl)cyclopentyl-4-heptenoic Acid
from Intermediate 10m. IR ($CHBr_3$) 3500, 1730, 1710 cm^{-1}.

q) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(4-thiomorpholinyl)cyclopentyl]-4-heptenoic Acid, S-dioxide
m.p. 113—115° from Intermediate 10n. Purification by chromatography using 98:2 through to 96:4 ER-methanol as eluent.

r) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-5-[[4'-methyl(1,1'-biphenyl)-4-yl]methoxy]-2-(4-thiomorpholinyl)cyclopentyl]-4-heptenoic Acid, S-dioxide
m.p. 119.5—121.5° from Intermediate 10o.

s) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-5-[4-(phenylmethyl)phenylmethoxy]-2-(4-thiomorpholinyl)cyclopentyl]-4-heptenoic Acid, S-dioxide
m.p. 127.5—128.5° from Intermediate 10p. Purification by chromatography using 96:4 ER-methanol as eluent.

t) [1α(Z),2β,3α,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-thiomorpholinyl)cyclopentyl]-4-heptenoic Acid, S-dioxide
m.p. 109.5—111.5° from Intermediate 10q. Purification by chromatography using 98:2 ER-methanol as eluent.

u) [1α(Z),2β,3α,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(hexahydro-1,4-oxazepin-4-yl)-3-hydroxycyclopentyl]-4-heptenoic Acid
from Intermediate 10r. TLC (SiO_2) 3:1 ER-methanol Rf 0.29.

v) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(1-piperidinyl)cyclopentyl]-4-heptenoic Acid, Compound with Piperazine (2:1)
m.p. 106—112° from Intermediate 10s. The *title compound* crystallised from a solution of the acid and piperazine in 2:1 EA-ER.

w) [1α(Z),2β,3α,5α]-(±)-7-[5-[3-[(1,1'-biphenyl)-4-yl]propoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid
from Intermediate 10t. Purification by chromatography using 5:1 EA-methanol as eluent. TLC 5:1 EA-methanol Rf 0.3.

x) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-5-[[3'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid
from Intermediate 10u. IR ($CHBr_3$) 3500, 1725 (sh.), 1710 cm^{-1}.

y) [1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-5-[[4'-methoxy(1,1'-biphenyl)-3-yl]methoxy]-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid
from Intermediate 10v. IR ($CHBr_3$) 3500, 1735 (sh.), 1710 cm^{-1}.

z) [1α(Z),2β,3α,5α]-(±)-7-[5-decyloxy-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid
from Intermediate 17d. IR ($CHBr_3$) 3500, 1735 (sh.), 1710 cm^{-1}.

Intermediate 13
[1α(Z),2β,3α,5α]-(±)-8-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-5-octenoic Acid

Prepared from Intermediate 6 (1 g) and (4-carboxybutyl)triphenylphosphonium bromide (3.17 g) in an analogous manner to that described for Intermediate 12a. The *title compound* was isolated as a foam (0.92 g). IR ($CHBr_3$) 3500, 1740, 1705 cm^{-1}.

Intermediate 14
[1α(Z),2β,3α,5α]-(±)-methyl 7-[5-[[1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-4-heptenoate

A solution of Intermediate 12a (0.7 g) in 9:1 methanol-H_2SO_4 (20 ml) was stirred at room temperature for 2 h. Solid $NaHCO_3$ was added until pH 7.5—8, followed by water and extraction with ER. The combined extracts were dried, filtered and evaporated to give the *title compound* as an oil (0.54 g). IR ($CHBr_3$) 3580—3510, 1730 cm^{-1}.

Intermediate 15
***(endo,anti)*-(±)-6-[[4'-methyl(1,1'-biphenyl)-4-yl]methoxy]-8-(4-morpholinyl)-2-oxabicyclo[3.2.1]octan-3-one**

Zinc bromide (27 g) in dry THF (180 ml) was stirred under nitrogen at 15—20° during the addition of p-methylphenylmagnesium bromide [prepared in ether (160 ml) from Mg (3.24 g) and 4-bromotoluene (20.52 g)]. The mixture was stirred at 20° for 2 h.

Nickel acetylacetonate (1.8 g) and triphenylphosphine (7.34 g) were taken into THF (40 ml) and stirred under nitrogen during the addition of DIBAL (1M in hexane, 7 ml). After 5 min Intermediate 72 (4.75 g) in THF (65 ml) was added followed, after a further 5 min by the organozinc reagent. The mixture was then stirred at 22° for 30 h, whereupon saturated NH_4Cl solution (500 ml) and EA (300 ml) were added. The aqueous solution was adjusted to pH 5—6 with 2N hydrochloric acid and the layers separated. The aqueous solution was extracted with EA and the combined extracts dried and evaporated. The residue was chromatographed on silica using 7:3 through to 9:1 EA-PE (b.p. 60—80°) as eluent to give the *title compound* (3.1 g) as prisms, m.p. 141—144°.

Intermediate 16
(1α,2β,3α,5α)-(±)-3-hydroxy-5-[[4'-methyl(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)cyclopentane Acetaldehyde

A stirred solution of Intermediate 15 (4.5 g) in dry CH_2Cl_2 (75 ml) at —75° under nitrogen was treated with DIBAL (1.43M in hexane, 17.4 ml). Stirring was continued for 1 h, whereupon methanol (75 ml) was carefully added and the temperature allowed to rise to ambient. After 17 h, the mixture was filtered and the filtrate evaporated to give the *title compound* as a foam (4.63 g). TLC 9:1 EA-methanol Rf 0.35.

Intermediate 17
a) (1α,2β,3α,5α)-(±)-3-hydroxy-5-[[4'-methyl(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)cyclopentanepropanal

To a stirred solution of potassium t-butoxide (3.89 g) in dry THF (110 ml) at —5° was added (methoxymethyl)triphenylphosphonium chloride (11.89 g) portionwise over 15 min. After stirring for 30 min at —5° to 0° a solution of Intermediate 16 (4.03 g) in dry THF (35 ml) was added. The mixture was stirred at 5° for 15 min and then at 20° for 1.75 h, quenched with water (7 ml) and the solvents removed *in vacuo*. The residue was then treated with 2N hydrochloric acid (20 ml) in acetone (50 ml) at 20° for 3.5 h. Aqueous Na_2CO_3 was added to give a solution of pH 8 which was then diluted with water (100 ml) and extracted with EA (3×75 ml). The combined extracts were dried and evaporated and the residue chromatographed on silica (400 g) using 97:3 through to 9:1 EA-methanol as eluent to give the *title compound* as an oil (4.33 g). IR (Neat) 3400 (br.), 1720 cm^{-1}.

The following compounds were prepared by a similar procedure:

b) (1α,2α,3α,5α)-(±)-5-[[1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentanepropanal
m.p. 114—116° from Intermediate 4c.

c) (1α,2β,3α,5α)-(±)-5-[[1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentanepropanal
from Intermediate 4e. IR ($CHBr_3$) 3500—3400 (br.), 1718 cm^{-1}.

d) (1α,2β,3α,5α)-(±)-5-decyloxy-3-hydroxy-2-(4-morpholinyl)cyclopentanepropanal
from Intermediate 4g. Purification by chromatography using EA through to 95:5 EA-methanol as eluents. IR (Neat) 3530, 1723 cm^{-1}.

Intermediate 18
[1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-5-[[4'-methyl(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid

(3-carboxypropyl)triphenylphosphonium bromide (12.9 g) was added to a solution of potassium t-butoxide (6.73 g) in dry THF (170 ml) and the resultant suspension stirred at 20° for 35 min. A solution of Intermediate 17a (4.23 g) in THF (40 ml) was added and stirring continued at 20° for 2 h. Water (5 ml) was then added, the solvent removed *in vacuo* and the residue taken into water (300 ml) and adjusted to pH 12 with 2N NaOH. Non-acidic material was extracted with EA (2×100 ml) and the

aqueous solution then re-adjusted to pH 6.5 with 2N hydrochloric acid. This solution was extracted with EA (3x100 ml) and the combined extracts dried and evaporated to give the *title compound* as an oil (3.97 g). IR ($CHBr_3$) 3580, 3500, 1720, 1710 cm^{-1}.

Intermediate 19

(1α,2β,3β,5β)-(±)-4-[3-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(3-methoxy-2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine

NaH (74% dispersion in oil, 316 mg) was added to a solution of Intermediate 8 (1.11 g) and 4-(bromomethyl)-4'-methoxy(1,1'-biphenyl) (2.86 g) in dry DMF (15 ml) under nitrogen at 0°. The mixture was stirred at room temperature for 2 h whereupon NaH (74%, 52 mg) was added and the stirring continued for 1 h. The mixture was poured into aqueous NH_4Cl (150 ml) and extracted with $CHCl_3$ (4x60 ml). The dried organic layers were evaporated and the residue chromatographed on silica (400 g) using 8:2 ER-PE (b.p. 60—80°) through to ER as eluent to give the *title compound* as an oil (1.17 g). IR ($CHBr_3$) 1675, 1245 cm^{-1}.

Intermediate 20

(1α,2β,3α,5α)-(±)-[3-hydroxy-5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)cyclopentanepropanal

A solution of Intermediate 19 (2.99 g) in 2N hydrochloric acid (25 ml), acetone (50 ml) and CH_2Cl_2 (7 ml) was stirred for 30 min. The mixture was poured into 8% $NaHCO_3$ solution (200 ml) and extracted with CH_2Cl_2 (3x85 ml). The dried organic layers were evaporated and the residue chromatographed on silica (100 g) using ER through to 4:1 ER-methanol as eluent to give the *title compound* as an oil (2.09 g). IR ($CHBr_3$) 3600—3500 (br.), 2725, 1720 cm^{-1}.

Intermediate 21

[1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-5-[[4'methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid

(4-carboxypropyl)triphenylphosphonium bromide (3.9 g) and potassium t-butoxide (2.04 g) in dry THF (90 ml) were stirred at room temperature for 15 min. A solution of Intermediate 20 (2 g) in dry THF (40 ml) was added and the mixture stirred for 2 h. Water (30 ml) was added and the solvent evaporated. The residue was poured into 0.3N NaOH (150 ml) and washed with EA. The basic layer was neutralised by the dropwise addition of 5N hydrochloric acid and then extracted with CH_2Cl_2 (70 ml). The pH was adjusted to 6.5 and the aqueous layer re-extracted with CH_2Cl_2 (70 ml). The combined CH_2Cl_2 layers were dried and evaporated to give the *title compound* as a foam (1.66 g) IR ($CHBr_3$) 3590, 3500, 1720 cm^{-1}.

Intermediate 22

a) Methyl 4-(thien-2-yl)benzoate

The Grignard reagent from 2-bromothiophene (17.5 g) and Mg (2.7 g) in dry ER (200 ml) was added to a stirred solution of anhydrous $ZnBr_2$ (22.5 g) in dry THF (200 ml) at 5°.

Simultaneously a solution of bis(triphenylphosphine)palladium (II) dichloride (1 g) in THF (200 ml) was treated with DIBAL in hexane (1.43M, 2 ml) at room temperature under nitrogen. After 5 min a solution of methyl p-bromobenzoate (5 g) in ER (50 ml) was added followed after a further 5 min by the organozinc reagent described above. The mixture was stirred at room temperature for 18 h and then poured into NH_4Cl solution and extracted with EA. The combined extracts were dried and evaporated, and the residue chromatographed on silica using 1:20 through to 1:1 EA-PE as eluent. The *title compound* was further purified by crystallisation from PE (b.p. 60—80°) (2.8 g), m.p. 141—142°.

The following compound was prepared in a similar manner:

b) Methyl 3'-methoxy(1,1'-biphenyl)-4-carboxylate

m.p. 52—54° from 3-bromoanisole and methyl p-bromobenzoate using the catalyst prepared from DIBAL, nickel acetylacetonate and triphenylphosphine. The product was purified by chromatography using 1:4 EA-PE (b.p. 60—80°) as eluent.

Intermediate 23

a) 4-(thien-2-yl)benzene Methanol

To a stirred suspension of $LiAlH_4$ (2.28 g) in THF (200 ml) at room temperature was added dropwise a solution of Intermediate 22a) (6.6 g) in THF (50 ml). The mixture was heated under reflux for 2 h and then stirred at room temperature for 16 h. EA (10 ml) was carefully added, followed by 2N hydrochloric acid (100 ml). The THF was removed *in vacuo* and the residue extracted with ER. The combined extracts were dried, filtered and concentrated. Crystallisation of the residue from cyclohexane gave the *title compound* (4.5 g) as plates, m.p. 115°.

The following compounds were prepared in a similar manner:

b) 3-[(1,1'-biphenyl)-4-yl]propanol

m.p. 73—74° from 3-[(1,1'-biphenyl)-4-yl]propanoic acid.

c) [3'-methoxy(1,1'-biphenyl)-4-yl]methanol
from Intermediate 22b. TLC EA Rf 0.6.

Intermediate 24
a) 2-(4-bromomethylphenyl)thiophene
A solution of Intermediate 23a (4.3 g) in dry CH_2Cl_2 (80 ml) was treated with a solution of PBr_3 (2.15 ml) in CH_2Cl_2 (20 ml) and the mixture stirred for 1 h. 10% $NaHCO_3$ solution (100 ml) was added, the organic phase separated, and the aqueous phase further extracted with CH_2Cl_2. The combined organic phase was dried, filtered and concentrated to give the *title compound* (4.6 g) as a solid, m.p. 80—100°.
The following compounds were prepared by a similar procedure:

b) 4-bromomethyl(1,1':4',1")terphenyl
m.p. 213—215° from 4-[(1,1':4',1")terphenyl]methanol.

c) 4-bromomethyl-3'-methoxy(1,1'-biphenyl)
from Intermediate 23c. TLC ER Rf 0.58.

Intermediate 25
a) [1α,(E),2β,3α,5α]-(±)-7-[3-hydroxy-5-[[4'-methyl(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid
A solution of Intermediate 18 (1.32 g) and p-toluene sulphinic acid (0.63 g) in dry 1,4-dioxan (60 ml) was heated under reflux in a nitrogen atmosphere for 3.5 h. The mixture was diluted with EA (80 ml), washed with pH 6 phosphate buffer (50 ml), dried and evaporated. The residue was chromatographed on silica using 9:1 EA-methanol as eluent to give the *title compound* as an oil, which on trituration with ER crystallised (0.63 g) m.p. 108—111°.
The following compounds was prepared in a similar manner:

b) [1α(E),2β,3α,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid
from Intermediate 12a. Purification by chromatography using 9:1 EA-methanol as eluent. TLC 85:15 ER-methanol Rf 0.24.

Intermediate 26
[1α(Z),2β,3α,5α]-(±)-7-[5-[[1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-4-heptenol
A solution of Intermediate 12a (1 g) in dry THF (10 ml) was added dropwise under nitrogen to a stirred suspension of $LiAlH_4$ (0.16 g) in dry THF (10 ml) and the mixture heated under reflux for 2 h. After cooling 1:1 water in THF (10 ml) was added followed by 5N NaOH (10 ml) and the mixture extracted with EA (3x20 ml). The combined extracts were dried, concentrated and the residue chromatographed on silica using 95:5 ER-methanol as eluent to give an oil which slowly crystallised (0.71 g). Recrystallisation from ER-isopentane gave the *title compound* of m.p. 70—71.5°.

Intermediate 27
***(anti,endo,endo)*-(±)-7-(4-morpholinyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]bicyclo[2.2.1]heptan-2-ol**
$NaBH_4$ (2.2 g) was added in portions to a stirred solution of Intermediate 69 (17 g) in dry methanol (250 ml) at 0°. After 30 min the mixture was poured into saturated NH_4Cl solution (350 ml) and extracted with ER (3x200 ml). The combined extracts were dried, filtered and concentrated to give the *title compound* as a foam (17.5 g). IR (Neat) 3440 (br.), 1120 cm^{-1}.

Intermediate 28
***(endo,syn,endo)*-(±)-5-[[(1,1'-biphenyl)-4-yl]methoxy]-7-(4-morpholinyl)bicyclo[2.2.1]heptan-2-ol**
A solution of Intermediate 2c (20.1 g) in 10% concentrated H_2SO_4 in methanol (60 ml) was stood at room temperature for 1 h. The solution was neutralised with solid $NaHCO_3$ and extracted with CH_2Cl_2 (3x200 ml). The combined extracts were dried, filtered and concentrated to give the *title compound* as a solid (17 g), m.p. 138—140°.

Intermediate 29
***(endo,syn)*-(±)-5-[[(1,1'-biphenyl)-4-yl]methoxy]-7-(4-morpholinyl)bicyclo[2.2.1]heptan-2-one**
A mixture of dry dimethylsulphoxide (13.5 ml) and dry CH_2Cl_2 (50 ml) was added under nitrogen to a solution of oxalyl chloride (15.2 ml) in dry CH_2Cl_2 (25 ml) at −78° and the resultant activated complex stirred for 15 min. A solution of Intermediate 28 (15 g) in dry CH_2Cl_2 (50 ml) was added dropwise and stirring continued for 5H. Triethylamine (55.1 ml) in dry CH_2Cl_2 (50 ml) was added dropwise and the mixture was then allowed to reach room temperature with further stirring for 1.5 h.

Water (350 ml) was added and the solution extracted with CH_2Cl_2 (3x200 ml). The combined extracts were dried, filtered and evaporated and the residue chromatographed on silica using ER as eluent. The *title compound* was obtained as a solid which was further purified by crystallisation from EA-PE (b.p. 60—80°) to give material (6.67 g) of m.p. 164—165°.

Intermediate 30
(*endo, syn*)-(±)-6-[[(1,1'-biphenyl)-4-yl]methoxy]-8-(4-morpholinyl)-2-oxabicyclo[3.2.1]octan-3-one

Peracetic acid (4.33 ml, 6.12 M) was added dropwise to a mixture of Intermediate 29 (2 g), sodium acetate (2.17 g), acetic acid (20 ml) and water (10 ml) at 0°. After stirring for 6 days a further quantity of peracetic acid (0.87 ml) was added and stirring continued for 24 h. Na_2SO_3 was added to destroy excess oxidising agent and the mixture was then evaporated to dryness. The residue was neutralised with 8% $NaHCO_3$ solution and extracted with EA (3x75 ml). The combined extracts were dried, filtered and evaporated and the residue chromatographed on silica using 1:1 ER-CH_2Cl_2 as eluent to give the *title compound* as a solid (1.5 g), m.p. 244—246°.

Intermediate 31
[1α(Z),2α,3α,5α]-(±)-methyl 7-[5-[[1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-4-heptenoate

Prepared as an oil from Intermediate 17a according to the methods described for Intermediates 12a and 14. IR (Neat) 3440 (br.), 1730 cm^{-1}.

Intermediate 32
[1α(Z),2α,3α,5α]-(±)-methyl 7-[3-(acetyloxy)-5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)cyclopentyl]-4-heptenoate

A solution of Intermediate 31 (1.2 g) and acetic anhydride (2 ml) in pyridine (10 ml) was heated at 45° for 18 h. The mixture was diluted with ER (50 ml) and then washed with 8% $NaHCO_3$ solution (150 ml). The aqueous solution was re-extracted with ER (100 ml) and the combined organic phase dried and concentrated. The residue was chromatographed on silica using ER as eluent to give the *title compound* as an oil (0.85 g). IR ($CHBr_3$) 1742 cm^{-1}.

Intermediate 33
a) [1α(Z),2α,3α,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid

A solution of Intermediate 32 (0.83 g) in methanol (30 ml) containing 2N NaOH (5 ml) was allowed to stand at room temperature for 2 days. pH 6.5 buffer (made from 2:3 KH_2PO_4:Na_2HPO_4) (30 ml) was added and the solution extracted with CH_2Cl_2 (2x50 ml). The combined extracts were dried and concentrated and the residue purified from CH_2Cl_2-PE (b.p. 60—80°) to give the *title compound* (0.61 g), m.p. 163—165°.

The following compound was prepared in a similar manner:

b) [1α(Z),2β,3α,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic Acid
from Intermediate 58. IR ($CHBr_3$) 3500, 1700, 1598 cm^{-1}.

Intermediate 34
[1α(Z),2β,3β,5α]-(±)-7-[5-[[1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid

a stirred solution of lithium tri-sec-butyl borohydride in THF (12 ml, 1 M) under nitrogen at —28° was treated slowly dropwise with a solution of Example 1a (0.6 g) in dry THF (12 ml). After 3 h the mixture was poured into 2N H_2SO_4 (20 ml) and pH 6.5 phosphate buffer (50 ml) and washed with ER (1x150 ml, 1x50 ml). The aqueous layer was adjusted to pH 6.5 with 2N NaOH and extracted with EA (2x100 ml). The combined extracts were dried and evaporated, and the residue chromatographed on silica using 4:1 EA-methanol as eluent to give the *title compound* as a foam (0.35 g). TLC (SiO_2) 1:20:79 acetic acid-methanol-EA Rf 0.17.

Intermediates 35 and 36
(1S,*endo*)-(+)-bicyclo[3.2.0]hept-2-en-6-ol (35) and (1R,*exo*)-(—)-bicyclo[3.2.0]hept-2-en-6-ol (36)

Bakers yeast (6 kg) and glucose (2.5 kg) in water (24 l) was stirred at 25° for 2 h. (±)-bicyclo[3.2.0]hept-2-en-6-one (120 g· was added dropwise over 30 min. Stirring was maintained for 2.5 h whereupon a further quantity of glucose (3.5 kg) and water (4 l) was added. This addition was repeated after 20 h and 26 h, glucose (4.5 kg) and water (5 l) being added on each occasion.

The reaction mixture was distilled at atmospheric pressure to give about 11 l of aqueous ethanol containing starting material and some product-Fraction A. Then a steam distillation of the remaining reaction mixture gave 36 l of aqueous distillate which was salted (7.25 kg) and extracted with CH_2Cl_2

(3x10 l). The CH_2Cl_2 was distilled at atmospheric pressure through a helix filled column (93x5 cm) to leave a residue (about 400 ml)-Fraction B. Fraction A was concentrated by distilling off most of the solvent through a helix filled column (50x3 cm). The residue was salted and extracted into CH_2Cl_2-Fraction C.

Fractions B and C were combined, dried and the solvent was removed at atmospheric pressure to leave a residue (55 g) which was distilled at 120°C and 15 mm Hg pressure to give an oil (39.8 g). This material was chromatographed on silica using 1:4 ether:isopentane as eluent to give the *title compound* as ethereal solutions after removal of most of the solvent.

Intermediate 35 (26.8 g) 64.5% w/w in ether.

Intermediate 36 (33.4 g) 30.4% w/w in ether.

The bulk of the material was used as above for the next stage. However 2 ml portions of the solutions were taken and distilled at atmospheric pressure in a micro distillation apparatus to give:

Intermediate 35 TLC 4:1 PE-ER Rf 0.3 $[\alpha]_D^{26}$=+46.1° ($CHCl_3$).

Intermediate 36 TLC 4:1 PE-ER Rf 0.2 $[\alpha]_D^{26}$=–73.9° ($CHCl_3$).

Intermediate 37

[1R-(*exo,endo*)]-(–)-2-bromo-3-hydroxybicyclo[3.2.0]heptan-6-one

To a stirred solution of Intermediate 35 (6.64 g) in acetone (220 ml) and water (55 ml) was added glacial acetic acid (0.65 ml) and N-bromosuccinimide (43.22 g) and stirring was maintained for 18 h. The mixture was poured into sodium thiosulphate solution (250 ml) and extracted with ER (2x175 ml). The organic layer was washed with 8% $NaHCO_3$ solution (150 ml), dried and evaporated and the residue chromatographed on silica using 1:1 ER-PE as eluent. The *title compound* was obtained as a solid which crystallised from CCl_4 as needles (4.16 g), m.p. 90—92°. $[\alpha]_D^{20}$=–60.8° (MeOH).

Intermediate 41

[1R-(*endo,anti*)]-(±)-5-hydroxy-7-(4-morpholinyl)bicyclo[2.2.1]heptan-2-one

A solution of Intermediate 37 (8.82 g) in CH_2Cl_2 (85 ml) containing morpholine (15 ml) was stirred at room temperature for 20 h. The precipitate was filtered off and washed with CH_2Cl_2 (100 ml). The combined filtrates were washed with $NaHCO_3$ solution and water (75 ml each) dried and evaporated to give a semi-solid which was chromatographed on silica using EA as eluent. The *title compound* was obtained as a solid which crystallised from 1:1 EA-PE (b.p. 60—80°) to give material (6.1 g) of m.p. 137—139°. $[\alpha]_D^{20}$=+55.73° (MeOH).

Intermediate 43

[1R-(*endo,anti*)]-(+)-5-[[(1,1'-biphenyl)-4-yl]methoxy]-7-(4-morpholinyl)bicyclo[2.2.1]heptan-2-one

A mixture of Intermediate 41 (10.45 g), benzyl triethylammonium chloride (1.5 g) and biphenylmethyl bromide (15.3 g) in CH_2Cl_2 (50 ml) was cooled to 0° whilst NaOH (12 g) in water (20 ml) was added. The two phases were stirred vigorously for 24 h at 20°. The mixture was diluted with water (120 ml) and extracted with CH_2Cl_2 (3x100 ml). The combined extracts were washed with brine (2x50 ml), dried and evaporated, and the residue triturated with ER (100 ml) to give a solid (16 g). The solid was crystallised from isopropyl acetate (120 ml) to give the *title compound* (9.6 g) as platelets m.p. 138—140°. $[\alpha]_D^{21}$=+22.12° ($CHCl_3$).

Intermediate 44

[1R-(*endo,anti*)]-(–)-6-[[(1,1'-biphenyl)-4-yl]methoxy]-8-(4-morpholinyl-2-oxabicyclo[3.2.1]octan-3-one

Peracetic acid (8.7 ml, 6.12 M) was added dropwise to a stirred solution of Intermediate 43 (5 g) in CH_2Cl_2 (25 ml) at 0°. The mixture was stirred for 24 h while allowing the temperature to rise to ambient. 20% w/w Na_2SO_3 in water (60 ml) was added dropwise at 0° and the mixture was stirred at room temperature for 0.75 h. Iso-propyl acetate (25 ml) was added and the layers were separated. The aqueous layer was extracted with (1:1) isopropyl acetate-CH_2Cl_2 (2x25 ml), and the combined organic layers were washed with 1N NaOH (2x50 ml) and brine (50 ml) then dried and evaporated to give a solid (3.3 g). The solid was crystallised from 1:1 EA-PE (80 ml) to give the *title compound* as prisms (6.9 g), m.p. 147—148°. $[\alpha]_D^{21.5}$=–26.44° ($CHCl_3$).

Intermediate 45

[1R-(1α,2β,3α,5α)]-5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentane Acetaldehyde

A solution of Intermediate 44 (3 g) in dry CH_2Cl_2 (60 ml) was cooled (–78°) and stirred under nitrogen whilst a solution of DIBAL in hexane (10.7 ml, 1.43 M) was added dropwise. Methanol (60 ml) was added dropwise at –78° and the cooling bath was removed. After stirring at room temperature for 2 h the precipitate was filtered off and was washed well with methanol. The combined filtrates were evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 (100 ml), dried, filtered and evaporated to give the *title compound* as a foam (2.95 g). IR ($CHBr_3$) 3580, 1718 cm^{-1}.

Intermediate 46
[1R-(1α,2β,3α,5α)]-5-[[1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentanepropanal

(Methoxymethyl)triphenylphosphonium chloride (7.15 g) was added to a stirred solution of potassium tert.-butoxide (2.35 g) in dry THF (40 ml) under nitrogen. After 15 min a solution of Intermediate 45 (2.75 g) in dry THF (20 ml) was added dropwise and stirring continued for 30 min.

The reaction mixture was poured into 2N hydrochloric acid (50 ml) at 0° and was stirred at 10—15° for 1.5 h. The mixture was adjusted to about pH 10 with saturated K_2CO_3 solution and extracted with CH_2Cl_2 (3×100 ml). The combined extracts were washed with brine (100 ml), dried and evaporated and the residue chromatographed on silica using 9:1 EA–methanol as eluent to give the *title compound* as a foam (2.47 g). TLC 9:1 EA–methanol Rf 0.3.

Intermediate 47
[1R-[1α(Z),2β,3α,5α]]-(+)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-4-heptenoic Acid, Hydrochloride

Dry THF (90 ml) was added to a stirred mixture of potassium *tert.*-butoxide (2.46 g) and 3-(carboxypropyl)triphenylphosphonium bromide (4.6 g) under nitrogen. After about 30 min Intermediate 46 (2.25 g) in dry THF (50 ml.) was added dropwise and stirring continued for 2.5 h. Water (25 ml) was added and most of the THF was removed *in vacuo.* The residue in water (50 ml) and 2N NaOH (20 ml) was extracted with EA (2×50 ml). The aqueous layer was adjusted to pH 6 with buffer (1 M KH_2PO_4 3 parts, 1 M Na_2HPO_4 1 part) and was extracted with CH_2Cl_2 (3×50 ml). The combined extracts were washed with brine, dried and evaporated to give a foam (2.7 g). This material was dissolved in EA (100 ml) and treated with an excess of ethereal hydrogen chloride. After cooling at 0° for 16 h the salt was collected and washed with 1:1 ER-EA (25 ml) followed by ER (40 ml). Crystallisation from 5:1 EA-methanol gave the *title compound* (1.6 g) as prisms, m.p. 152—153°. $[\alpha]_D^{21}$=+54° ($CHCl_3$).

Intermediate 48
(1α,2β,3β,5β)-(±)-4-[2-(3-methoxy-2-propenyl)-3-[(2-phenylthien-4-yl)methoxy]-5-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]morpholine

NaH (0.952 g, 50% in oil) was added to a stirred solution of Intermediate 76 (5.38 g) and Intermediate 8 (2.6 g) in DMF (15 ml) at 0°. Stirring at room temperature was continued for 2 h whereupon saturated NH_4Cl solution (50 ml) was added and the mixture extracted with ER (3×50 ml). The combined extracts were washed with water (2×100 ml), brine (100 ml) and then dried. Evaporation gave an oil which was chromatographed on silica using 19:1 ER-methanol as eluent to give the *title compound* (2.87 g).

Analysis Found:	C, 68.1;	H, 7.8;	N, 2.7
$C_{29}H_{38}NO_5S$ requires:	C, 68.0;	H, 7.4;	N, 2.7%

Intermediate 49
(1α,2β,3α,5α)-(±)-3-hydroxy-2-(4-morpholinyl)-5-[(2-phenylthien-4-yl)methoxy]cyclopentanepropanal

A solution of Intermediate 48 (2.75 g) in acetone (20 ml) was treated with 2N hydrochloric acid (10 ml) for 2 h. 2N Na_2CO_3 solution (10 ml) was then added and the acetone removed *in vacuo.* The remaining solution was basified by adding more Na_2CO_3 solution and the mixture was extracted with ER (3×30 ml). The combined organic layers were washed with brine (20 ml), dried and concentrated. The residue was chromatographed on silica using 9:1 ER-methanol as eluent to give the *title compound* as a foam (2 g).

Analysis Found:	C, 66.3;	H, 7.0;	N, 3.3
$C_{23}H_{29}NO_4S$ requires:	C, 66.5;	H, 7.0;	N, 3.4%

Intermediate 50
[1α(Z),2β,3α,5α]-(±)-7-[3-hydroxy-2-(4-morpholinyl)-5-[(2-phenylthien-4-yl)methoxy]cyclopentyl]-4-heptenoic Acid

To an intimate mixture of potassium t-butoxide (1.89 g) and (3-carboxypropyl)triphenylphosphonium bromide (3.62 g) under nitrogen was added dry THF (50 ml). The suspension formed was stirred for 30 min whereupon a solution of Intermediate 49 (1.75 g) in dry THF (10 ml) was added in one portion. Stirring was maintained for 1 h whereupon water (40 ml) and $NaHCO_3$ solution (10 ml) were added and the mixture extracted with ER (3×50 ml). The extracts were discarded and the aqueous phase acidified to pH 6.5 with KH_2PO_4 solution and extracted with ER (3×75 ml). The combined ethereal extracts were washed with water (50 ml), brine (50 ml) and then dried. After evaporation the residue was chromatographed on silica using 4:1 ER-methanol as eluent to give the *title compound* as a foam (1.15 g).

Analysis Found: C, 66.8; H, 7.3; N, 3.0
$C_{27}H_{35}NO_5S$ requires: C, 66.8; H, 7.3; N, 2.9%

Intermediate 51
(*endo,anti*)-(±)-7-azido-5-hydroxybicyclo[2.2.1]heptan-2-one

A solution of (*exo,endo*)-(±)-3-acetoxy-2-bromobicyclo[3.2.0]heptan-6-one (50 g) and potassium t-butoxide (27.25 g) in THF (1.5 l) was stirred at —75° for 1 h. The solution was allowed to warm to 0° and a solution of sodium azide (16.45 g) in water (600 ml was added and stirring continued at 20° for 18 h.

The two layers were separated and ether was added to the organic layer which was washed with water (2×250 ml). The combined aqueous layers were extracted with ER (2×250 ml) The combined organic layers were dried and evaporated to give a gum (28.1 g). A solution of the gum in methanol (225 ml) was stirred with K_2CO_3 (18.37 g) for 3.5 h at room temperature. The mixture was filtered and the filtrate was evaporated *in vacuo* to give a solid which was then taken into ER (150 ml) and washed with water (150 ml). The aqueous layer was extracted with ER (3×125 ml) and the combined organic layers were dried and evaporated to give an oil (24.5 g) which was chromatographed on silica. Elution with 2:1 ER-PE gave an oil (18.7 g) which was triturated with ER to give the *title compound* as a solid (14.6 g), m.p. 72—74°.

Intermediate 52
(3aα,4β,5α,6aα)-(±)-4-azido-hexahydro-5-hydroxy-2H-cyclopenta(b)furan-2-one

40% Peracetic acid (64.35 ml) was added to a cooled (0°) stirred solution of Intermediate 51 (12.9 g) and sodium acetate (31.2 g) in acetic acid (155 ml) and water (15.5 ml) and the resulting solution then stirred at ambient temperature for 24 h. Excess NA_2SO_3 solution was added to the cooled solution and stirring continued for 1 h. After evaporation *in vacuo* the residue was dissolved in 5N NaOH solution (400 ml) with cooling and the solution stirred for 0.5 h. Concentrated hydrochloric acid (30 ml) was added with cooling and the solution was continuously extracted with CH_2Cl_2 (600 ml) for 18 h. The organic extracts were washed with 2N Na_2CO_3 solution (100 ml) and brine (100 ml), dried and evaporated to give a solid (3.5 g). A portion (1 g) was recrystallised from ER-PE (b.p. 60—80°) to give the *title compound* (816 mg), m.p. 73—74°.

Intermediate 53
(3aα,4β,5α6aα)-(±)-4-azido-hexahydro-5-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-cyclopenta(b) furan-2-one

Dihydropyran (6.1 ml) was added to a cold (—20°) stirred solution of p-toluenesulphonic acid (0.685 g) and Intermediate 52 (6.63 g) in CH_2Cl_2 (35 ml). After 2 h at —20° the mixture was poured into 8% $NaHCO_3$ solution (300 ml). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×100 ml). The combined extracts were washed with brine (200 ml), dried and evaporated *in vacuo* to give an oil (13.23 g) which was purified by chromatography on silica. Elution with 2:1 ER-PE (b.p. 60—80°) gave the *title compound* as an oil (5.39 g). IR (Neat) 2100, 1780 cm^{-1}.

Intermediate 54
(3aα,4β,5α,6aα)-(±)-4-amino-hexahydro-5-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-cyclopenta(b)furan-2-one

A solution of Intermediate 53 (28.4 g) in ethanol (175 ml) was hydrogenated at atmospheric pressure over pre-reduced 10% palladium oxide on charcoal (5.3 g) at 20° for 24 h. The mixture was filtered ('Hyflo') and the filtrate evaporated to give an oil (24.1 g). IR ($CHBr_3$) 3370, 3300, 1762 cm^{-1}.

Intermediate 55
a) (3aα,4α,5β,6aα)-(±)-hexahydro-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-(4-thiomorpholinyl)-2H-cyclopenta(b)furan-2-one

A mixture of Intermediate 54 (6 g), anhydrous $NaHCO_3$ (5.2 g), NaI (9.72 g) and bis(2-chloroethyl)sulphide (5.15 g) in acetonitrile (250 ml) was heated under reflux for 18 h. The solvent was removed *in vacuo* and the residue in water (200 ml) was extracted with EA (4×200 ml). The combined extracts were washed with brine (200 ml), dried and evaporated to give an oil (10.2 g) which was purified by chromatography on silica. Elution with ER and then 3:97 methanol-ER gave a solid (4.8 g). A portion was crystallised from ER-PE to give the *title compound,* m.p. 83—84°.

The following compound was prepared in a similar manner:

b) (3aα,4α,5β,6aα)-(±)-4-(hexahydro-1,4-oxazepin-4-yl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-cyclopenta(b)furan-2-one

m.p. 68.5—72.5° from Intermediate 54. Purification by chromatography using 85:15 ER-methanol as eluent.

Intermediate 56
(*anti,endo*)-(±)-7-(1-piperidinyl)-5-[(tetrahydro -2H-pyran-2-yl)oxy]bicyclo[2.2.1]heptan-2-one

Piperidine (64.1 ml) was added dropwise to a solution of (*exo,endo*)-(±)-2-bromo-3-[(tetrahydro-2H-pyran-2-yl)oxy]bicyclo[3.2.0]heptan-6-one (75 g) in high purity acetone (250 ml) at 0°. The

mixture was stirred in the dark for 24 h and then filtered. The filtrate was washed with water (2x150 ml), and the aqueous solution extracted with ER (3x200 ml). The combined organic layers were dried, filtered and evaporated to give the *title compound* as an oil (77.2 g). TLC 7:3 ER-PE Rf 0.18.

Intermediate 57
(*endo,anti*)-(±)-5-hydroxy-7-(1-piperidinyl)bicyclo[2.2.1]heptan-2-one, Hydrochloride

Ethereal hydrogen chloride (20 ml) was added dropwise to a solution of intermediate 56 (77.2 g) in methanol (300 ml) at 0°. After stirring for 1.5 h at room temperature the solvent was removed *in vacuo,* and the residue triturated with iso-propanol to give the *title compound* as a solid (52 g), m.p. 246—248°.

Intermediate 58
[1α(Z),2β,3α,5α]-(±)-methyl 7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoate

Prepared as an oil from Intermediate 17c according to the methods described for Intermediates 12a and 14. Purification by chromatography using 9:1 EA-methanol as eluent. IR ($CHBr_3$) 3520, 1725, cm^{-1}.

Intermediate 59
a) (1α,2α,3β,4α)-(±)-2-(3-methoxy-2-propenyl)-4-[(tetrahydro-2H-pyran-2-yl)oxy]-3-(4-thiomorpholinyl)cyclopentanol, S-dioxide

A solution of Intermediate 7b (12.1 g) in methanol (80 ml) containing 1N NaOH (60 ml) was stirred at room temperature for 5 h. The mixture was poured into brine (650 ml) and extracted with CH_2Cl_2 (5x150 ml). The combined extracts were dried, filtered and concentrated to give an oil, which was chromatographed on silica using 13:7 EA-PE (b.p. 60—80°) through to EA as eluent to give the *title compound* as an oil (8.38 g). IR (Neat) 3510 (br.), 1650 cm^{-1}.

The following compound was prepared by a similar procedure:

b) (1α,2α,3β,4α)-(±)-3-(hexahydro-1,4-oxazepin-4-yl)-2-(3-methoxy-2-propenyl)-4-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentanol
from Intermediate 7c IR ($CHBr_3$) 3500, 1655 cm^{-1}.

Intermediate 60
3-[(1,1'-biphenyl)-4-yl]propanol, 4-methylbenzenesulphonate

A stirred solution of Intermediate 23b (4.28 g) in pyridine (40 ml) at 0° was treated portionwise with p-toluene sulphonyl chloride (7.71 g) over 1h. Stirring was continued at 0° for 7 h when water (20 ml) was added and the mixture allowed to warm to room temperature with stirring for a further 1 h. The mixture was partitioned between 2N.H_2SO_4 (250 ml) and ER (250 ml), the layers separated and the organic phase washed with a further quantity of 2N.H_2SO_4 (2x250 ml). The organic phase was then washed with 2N.NaOH (3x100 ml), water (2x100 ml) and dried. Evaporation of the solvent gave the *title compound* as a solid (4.95 g), m.p. 86—87°.

Intermediate 61
(3aα,4α,5β,6aα)-(±)-hexahydro-5-hydroxy-4-(4-thiomorpholinyl)-2H-cyclopenta(b)furan-2-one, S-dioxide, Hydrochloride

A solution of (*endo,anti*)-(±)-6-(phenylmethoxy)-8-(4-thiomorpholinyl)-2-oxabicyclo[3.2.1]octan-3-one, S-dioxide (10 g) in ethanol (60 ml) and water (40 ml) containing concentrated hydrochloric acid (40 ml) was hydrogenated over pre-reduced 10% palladium oxide on charcoal (5 g, 50% dispersion in water) in ethanol (40 ml). The mixture was filtered and the filtrate evaporated *in vacuo* to give the *title compound* as a solid (8.55 g), m.p. above 230° (dec.) (from water-ethanol).

Intermediate 62
(3aα,4α,5β,6aα)-(±)-hexahydro-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-(4-thiomorpholinyl)-2H-cyclopenta(b)furan-2-one, S-dioxide

Dihydropyran (3.1 ml) was added to a stirred solution of the free base of Intermediate 61 (1.56 g) and p-toluene sulphonic acid monohydrate (1.17 g) in dry DMF (30 ml) at −10°. The mixture was allowed to reach ambient temperature and stirring continued for 18 h, whereupon it was poured into saturated aqueous $NaHCO_3$ solution (50 ml), extracted with EA (4x100 ml), washed with water, dried, filtered and concentrated. The residue was chromatographed using 19:1 ER-methanol as eluent to give the *title compound* as a viscous oil (1.89 g. IR ($CHBr_3$) 1762 cm^{-1}.

Intermediate 63
(3aα,4α,5β,6aα)-(±)-hexahydro-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-(4-thiomorpholinyl)-2H-cyclopenta(b)furan-2-ol, S-dioxide

A solution of Intermediate 62 (1 g) in CH_2Cl_2 (25 ml) at −70° under dry nitrogen was stirred during the additon of DIBAL (1 M in hexane, 8.7 ml). After 1.5 h at −70°, methanol (25 ml) was

carefully added and the mixture was then allowed to rise to ambient temperature whereupon stirring was continued for 18h. The mixture was filtered through 'Hyflo' and the filtrate evaporated to give the *title compound* as an oil (0.95 g).

Analysis Found:	C, 53.2;	H, 7.6;	N, 3.5	
$C_{16}H_{27}NO_6S$ requires:	C, 53.2;	H, 7.5;	N, 3.9%	

Intermediate 64

4-phenyl-2-thiophenemethanol

A stirred suspension of 4-phenyl-2-thiophenecarboxaldehyde (4.32 g) in absolute ethanol (85 ml) was cooled in an ice-bath and treated with $NaBH_4$ (1.06 g). After 20 min the mixture was allowed to attain ambient temperature when stirring was continued for 6 h. Saturated aqueous NH_4Cl (30 ml) was then carefully added to the vigorously stirred mixture, and the resulting suspension extracted with ER (2×200 ml). The combined extracts were dried (Na_2SO_4/K_2CO_3), filtered and evaporated to give the *title compound* (4.2 g) as crystals, m.p. 112—113°.

Intermediate 65

2-(bromomethyl)-4-phenylthiophene

A cooled, stirred suspension of Intermediate 64 (3.86 g) in dry CH_2Cl_2 (60 ml) was treated dropwise with a solution of PBr_3 (1.27 ml) in dry CH_2Cl_2 (20 ml), and stirring continued for 30 min. The mixture was treated with 8% aqueous $NaHCO_3$ (100 ml), stirred for 20 min, extracted with ER (1×150 ml, 1×50 ml), and the extracts dried ($MgSO_4$), filtered and evaporated to give the *title compound* (5.01 g) as a solid, m.p. 87—88.5°.

Intermediate 66

[4'-methyl(1,1-biphenyl)-4-yl]methanol

4-methyl(1,1'-biphenyl)-4-carboxylic acid, methyl ester (1.43 g) in ER (25 ml) and THF (25 ml) was added over 5 min to $LiAlH_4$ (420 mg) in ER (25 ml). The mixture was stirred at room temperature for 1 h and then cooled in ice. Aqueous NaOH (1M, 2.1 ml) was added and after stirring (15 min) excess anhydrous Na_2SO_4 was added. The mixture was filtered and the filtrate evaporated to give a solid. Crystallisation from cyclohexane-methanol gave the *title compound* (1.04 g) m.p. 128—31°.

Intermediate 67

4-bromomethyl-4'-methyl (1,1'-biphenyl)

To a cold (0°) solution of Intermediate 66 (0.917 g) in dry CH_2Cl_2 (14 ml) was added PBr_3 (0.29 ml).

After stirring for 1 h at 0°, 8% $NaHCO_3$ solution (30 ml) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2×30 ml), dried and evaporated to give a solid (0.99 g). Crystallisation from PE (b.p. 60—80°) afforded the *title compound* (0.91 g) m.p. 100—102°.

Intermediate 68

4-bromomethyl-4'-chloro-1,1'-biphenyl

4'-chloro(1,1'-biphenyl)-4-methanol (5.8 g) was converted into the *title compound* (6.8 g), m.p. 64—66° by the method for the preparation of Intermediate 67.

Intermediate 69

(±)-7-*anti*-(4-morpholinyl)-5-*endo*-[tetrahydro-2H-pyran-2-yl)oxy]bicyclo[2.2.1]heptan-2-one

Morpholine (76 ml) was added dropwise over 15 mins to a stirred solution of 2-exo-bromo-3-endo-[(tetrahydro-2H-pyran-2-yl)oxy]bicyclo[3.2.0]heptan-6-one (100.8 g) in acetone (500 ml) at 0°. After 2 h at 5° the mixtures was stirred at 20° for 18 h and then filtered. Evaporation of the filtrate gave an oil which was taken into ER (350 ml), filtered and washed (water, 2×100 ml). The ethereal solution was dried, filtered and evaporated to give the *title compound* as a solid. Purification from PE gate material (85.5 g) of m.p. 86—88°.

Intermediate 70

(±)-5-*endo*-hydroxy-7-*anti*-(4-morpholinyl)bicyclo[2.2.1]heptan-2-one, Hydrochloride

To a stirred solution of Intermediate 69 (96.4 g) in methanol (600 ml) was added an ethereal solution of HCl (240 ml) and the mixture stirred at 20° for 2.5 h (pH 1.5—2). Filtration followed by evaporation of the filtrate gave an oil which solidified on trituration with EA (2×200 ml). Coloured impurities were removed by extraction with boiling isopropanol to leave the *title compound* as a solid (70.6 g), m.p. 181—182°.

Intermediate 71

(±)-5-*endo*-(4-bromophenylmethoxy)-7-*anti*-(4-morpholinyl)bicyclo[2.2.1]heptan-2-one

Aqueous NaOH solution (10 N; 200 ml) was added to a solution of the free base of Intermediate 70 (21.1 g), benzyltriethylammonium chloride (4 g) and 4-bromobenzyl bromide (27.5 g) in CH_2Cl_2

(400 ml) and the mixture stirred vigorously for 4 h. A further portion of 4-bromobenzylbromide (9 g) was then added and stirring continued for 68 h. Water (200 ml) was added and the layers separated. The aqueous layer was extracted with EA (2x75 ml), washed with water, dried and evaporated to give an oil (48 g) which solidified on standing. Excess alkylating agent was removed by triturtion with PE (b.p. 60—80°) and crystallisation from EA-PE (b.p. 60—80°) then gave the *title compound* (34.1 g) as a solid, m.p. 130—131°.

Intermediate 72
(±)-6-*endo*-(4-bromophenylmethoxy)-8-*anti*-(4-morpholinyl)-2-oxabicyclo[3.2.1]octan-3-one

Intermediate 71 (13.2 g) in acetic acid (110 ml) and water (55 ml) containing $CH_3COONa \cdot 3H_2O$ (23.7 g) was cooled (*ca.* 5—10°) and stirred during the dropwise addition of peracetic acid (6.1M; 28.5 ml). The resulting solution was stirred at 20° for 48 h when 10% Na_2SO_3 solution (200 ml), was added, maintaining the temperature of the mixture at 10—15°. After 1.5 h solvents were removed *in vacuo* at 35°, the residue taken into water (150 ml) and basified to pH 9 with Na_2CO_3 solution. Extraction with EA (3x200 ml) followed by drying and evaporation gave a solid which crystallised from EA to give the *title compound* (5.49 g), m.p. 154—156°.

Intermediate 73
4-(1,3-dioxolan-2-yl)-2-phenylthiophene

A solution of 5-bromo-3-thiophenecarboxaldehyde (32.5 g) in benzene (500 ml) was treated with p-toluenesulphonic acid monohydrate (0.323 g) and ethylene glycol (21.1 g), and the mixture heated under reflux in a Dean and Stark apparatus until the theoretical volume of water had been removed. After cooling the mixture was washed with water, (2x) then brine, dried, filtered and concentrated, and the residue distilled (b.p. 96—100° at 0.4 mm) to give the *title compound* as an oil (24 g).

Analysis Found:	C, 35.8;	H, 3.0
$C_7H_7BrO_2S$ required:	C, 35.7;	H, 3.0%

Intermediate 74
5-phenyl-3-thiophenecarboxaldehyde

A solution of phenylmagnesium chloride in THF (82.94 ml, 2.39 M) was added to a stirred solution of $ZnBr_2$ (44.6 g) in dry THF (350 ml) under nitrogen. The mixture was stirred at room temperature for 15 min.

DIBAL (9.91 ml, 1 M) in hexane solution was added dropwise to a stirred mixture of triphenylphosphine (10.39 g) and nickel acetoacetonate (2.55 g) in dry THF (160 ml) under nitrogen. A solution of Intermediate 73 (23.3 g) in dry THF (150 ml) was added after 10 min. The solution containing the organozinc reagent was then added dropwise and the mixture was stirred for 1 h.

2N hydrochloric acid (400 ml) was added at 0° and the mixture was stirred at room temperature for 0.5 h. The two layers were separated and the aqueous layer was extracted with ER (2x400 ml), washed with $NaHCO_3$ solution and brine and then dried. Solvent removal *in vacuo* gave a solid (32.8 g) which was chromatographed using 9:1 PE (b.p. 60—80°)-EA or eluent to give the *title compound* (13.35 g), m.p. 64—65° (from PE (b.p. 60—80°)).

Intermediate 75
5-phenyl-3-thiophenemethanol

A stirred solution of Intermediate 74 (12 g) in methanol (120 ml) was treated with $NaBH_4$ (1.82 g) at room temperature for 15 min. The mixture was cooled to 0° and treated with NH_4Cl solution (200 ml), followed by water (200 ml) and ER (400 ml). The ER extract was separated and the aqueous phase further extracted with ER (400 ml), washed with brine, dried, filtered and evaporated to afford the *title compound* as a solid (11.5 g), m.p. 92—93°.

Intermediate 76
4-(bromomethyl)-2-phenylthiophene

Intermediate 75 was converted into the *title compound* by the method for the preparation of Intermediate 65. TLC (ER) Rf 0.58.

Intermediate 77
[1α(Z/E),2β,3α,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-4-bromo-4-heptenoic Acid

To a stirred solution of potassium *tert*-butoxide (6.06 g) in dry THF (140 ml) at −70° was added (4-carbethoxypropyl)triphenylphosphonium bromide (22.16 g). After 0.5 h at −70° a solution of bromine in CH_2Cl_2 (25% v/v, 6.7 ml) was added dropwise and then stirring maintained for 0.9 h. A solution of Intermediate 6 (4.09 g) in THF (30 ml) was then added and, after 0.5 h, the temperature of the mixture allowed to rise to 0° over 1 h. 2N NaOH (60 ml) and methanol (60 ml) were added and stirring continued at 20° for 4 h. After evaporation *in vacuo* the residue was taken into water (200 ml) and adjusted to pH 12 with 2N NaOH. Non-acidic material was removed by extraction with EA (1x100

ml, 2×50 ml), and the aqueous phase then re-adjusted to pH 6 with 2N hydrochloric acid. Extraction with EA (4×60 ml), drying and concentration gave the *title compounds* as a foam (5.23 g). IR ($CHBr_3$) 3500, 1725, 1710 cm^{-1}.

Intermediate 78
(1α,2β,3α,5α)-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(4-morpholinyl)cyclopentyl]-4-heptynoic Acid, Hydrochloride

To a stirred solution of Intermediate 77 (2 g) in THF (15 ml) at 0° was added potassium *tert*-butoxide (2.4 g) in DMSO (15 ml). The mixture was stirred at 0° for 0.5 h and at 20° for 1.5 h whereupon water (200 ml) was added and the mixture extracted with EA (1×50 ml). The aqueous solution was adjusted to pH 6 with 2N hydrochloric acid and extracted with EA (3×60 ml). The combined extracts were washed with water (3×60 ml), dried and evaporated to give an oil, which was purified by chromatography on silica (130 g) using 4:1 EA-methanol as eluent to give a foam (0.65 g). A sample was treated with ethereal hydrogen chloride to give the *title compound*. Crystallisation from EA gave material of m.p. 162—163.5.

Intermediate 79
(1α,2β,5α)-(±)-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxo-cyclopentyl]-4-heptynoic Acid

Prepared from the free base of Intermediate 78 according to the procedure described for Example 3a. Purification by chromatography using ER through to 98:2 ER-methanol as eluent. Crystallisation from ER-PE (b.p. 60—80°) gave material of m.p. 90—93°.

Intermediate 80
***(endo,anti)*-(±)-5-decyloxy-7-(4-morpholinyl)bicyclo[2.2.1]heptan-2-one**

Sodium hydride (46% dispersion in oil, 0.522 g) was added portionwise over 10 min to a stirred solution of Intermediate 1 (1.06 g) and decyl tosylate (2.34 g) in dry DMF (10 ml) under dry nitrogen at room temperature. The mixture was stirred for 5 h, poured into water (50 ml) and extracted with ER (50 ml, 2×25 ml). The combined extracts were washed with water (25 ml), dried and concentrated to give a solid. Crystallisation from PE gave the *title compound* (0.59 g), m.p. 64—65°.

Example 1
a) [1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid

Method 1

To a cold (−11°) stirred solution of Intermediate 12a) (920 mg) and triethylamine (2.14 ml) in CH_2Cl_2 (10 ml) and DMSO (10 ml) was added pyridine-sulphur trioxide complex (915 mg) in DMSO (10 ml). Stirring was maintained at 25°C for 3 h whereupon water (10 ml) was added and the CH_2Cl_2 evaporated. To the resulting suspension a solution of citric acid (1.07 g) in water (10 ml) was added. The mixture was extracted with EA, the combined extracts dried and concentrated. The residual oil was chromatographed on silica using ER as eluent to give the *title compound* as an oil which slowly crystallised (0.37 g). Recrystallisation of a sample from ER-iso-pentane at 0° gave material of m.p. 77.5—80°, IR (Nujol) 3350—2400 (br.), 1735, 1705 cm^{-1}; whereas recrystallisation above 5° gave a different polymorphic form of m.p. 98—100.5°, IR (Nujol) 3400—2300 (br.), 1735, 1702, 1250, 1005 cm^{-1}.

Analysis Found:	C, 72.9;	H, 7.4;	N, 2.9
$C_{29}H_{35}NO_5$ requires:	C, 72.9;	H, 7.4;	N, 2.9%

Method 2

Jones reagent (0.54 ml, 2.67 M) was added to a mixture of Intermediate 26 (0.25 g) and 'Hyflo' (1 g) in acetone (10 ml) and stirred for 1H. Isopropanol (1 ml) was added, the mixture filtered and the filtrate washed with pH 5 buffer (2×10 ml). After drying and evaporation the residue was purified by chromatography on silica using ER as eluent to give the *title compound* (0.024 g).

Method 3

From Intermediate 33a) by the procedure described under Method 2.

Method 4

From Intermediate 34 by the procedure described under Method 2.

Method 5

A suspension of 5% Pd on $CaCO_3$ poisoned with lead (70 mg) in EA (5 ml) containing triethylamine (0.2 ml) was hydrogenated at 21° and atmospheric pressure for 0.5 h. A solution of Intermediate 79 (36 mg) in EA (4 ml) was added and the hydrogenation continued for 2 h. The mixture was filtered, diluted with ER (20 ml) and washed with pH 6 phosphate buffer solution (30 ml).

Evaporation of the dried ethereal solution gave a solid (35 mg) which crystallised from ER-PE (b.p. 60—80°) to give the *title compound* (23 mg), m.p. 95—98°.

The following compounds were prepared by the procedure described for Method 1.

b) [1α(Z),2β,5α]-(±)-8-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-5-octenoic Acid
m.p. 118—120° from Intermediate 13.

Analysis Found:	C, 73.6;	H, 7.7;	N, 2.9	
$C_{30}H_{37}NO_5$ requires:	C, 73.3;	H, 7.6;	N, 2.9%.	

c) [1α(Z),2β,5α]-(±)-7-[2-(4-morpholinyl)-5-(2-naphthalenylmethoxy)-3-oxocyclopentyl]-4-heptenoic Acid
from Intermediate 12b. Purification by chromatography using ER as eluent. IR ($CHBr_3$) 3600—2300 (br.), 1735, 1702 cm^{-1}

Analysis Found:	C, 71.1;	H, 7.5;	N, 3.2	
$C_{27}H_{35}NO_5$ requires:	C, 71.8;	H, 7.4;	N, 3.1%	

d) [1α(Z),2β,5α]-(±)-7-[5-[4-(1,1-dimethylethyl)phenylmethoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid
from Intermediate 12d. Purification by chromatography using ER as eluent. IR ($CHBr_3$) 3500, 1738, 1705 cm^{-1}. TLC 95:5 ER-methanol R_f 0.53.

e) [1α(Z),2β,5α]-(±)-7-[5-[4-methylthiophenylmethoxy)]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid, Compound with Piperazine
(2:1), from Intermediate 12j. The acid was purified by chromatography using ER as eluent. The *title compound* (106 mg) crystallised from a solution of the acid (168 mg) and piperazine (25 mg) in ER (5 ml) to give material of m.p. 75—76.5°. IR ($CHBr_3$) 1735, 1590 cm^{-1}.

f) [1α(Z),2β,tα]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-oxo-2-(4-thiomorpholinyl)cyclopentyl]-4-heptenoic Acid
from Intermediate 12p. Purification by chromatography using 7:3 ER-isopentane as eluent. IR ($CHBr_3$) 3500, 1740, 1705 cm^{-1}. TLC ER R_f 0.45.

g) [1α(Z),2β,5α]-(±)-7-[5-[[4'-methoxy(1,1'-biphenyl)-3-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid
from Intermediate 12y. Purification by chromatography using 4:1 EA-PE (b.p. 60—80°) as eluent. IR ($CHBr_3$) 3500, 1740, 1710 cm^{-1}. TLC 4:1 EA-PE (b.p. 60—80°) Rf 0.44.

Example 2
[1α(Z),2β,5α]-(±)-methyl 7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoate

To a cold (—60°), stirred solution of oxalyl chloride (0.144 ml) in dry CH_2Cl_2 (20 ml) was added DMSO (0.133 ml). The solution was stirred for 15 min, when a solution of Intermediate 14 (0.37 g) in dry CH_2Cl_2 (20 ml) was added. After stirring for 2 h, triethylamine (1.04 ml) in dry CH_2Cl_2 (5 ml) was added and the temperature then allowed to rise to ambient over 0.75 h. ER was then added and the mixture washed with 8% $NaHCO_3$ solution. The organic phase was separated, dried and concentrated, and the residue chromatographed on silica. Elution with 3:1 ER-isopentane gave the *title compound* as an oil (0.23 g). IR ($CHBr_3$) 1730 cm^{-1}.

Analysis Found:	C, 73.1;	H, 7.0;	N, 2.8	
$C_{30}H_{37}NO_5$ requires:	C, 73.3;	H, 7.6;	N, 2.9%	

Example 3

a) [1α(Z),2β,5α]-(±)-7-[5-[4-methoxy(phenylmethoxy)]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid, Compound with Chloroform (3:1)

To a solution of Intermediate 12c) (0.18 g) in acetone (10 ml) at —5° was added 'hyflo' (0.7 g) followed by Jones reagent (2.67 M, 0.36 ml). The temperature was allowed to rise to 5° during 45 min when isopropanol (1 ml) was added. After 5 min the mixture was filtered and the solid washed thoroughly with ER. The combined organic layers were washed with pH 6.5 phosphate buffer (2×20 ml), dried and concentrated. Purification by chromatography using 98:2 $CHCl_3$-methanol as eluent gave the *title compound* as an oil (0.06 g). IR ($CHBr_3$) 3500, 1740, 1710 cm^{-1}. TLC 98:2 $CHCl_3$-methanol. Rf 0.4.

The following compounds were prepared using a similar procedure:

b) [1α(Z),2β,5α]-(±)-7-[5-[[4'-chloro(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid
from Intermediate 12h. Purification by chromatography using 99:1 $CHCl_3$-methanol as eluent. IR ($CHBr_3$) 3490, 1740, 1705 cm^{-1}.

Analysis Found:	C, 67.7;	H, 6.6;	N, 2.8	
$C_{29}H_{34}ClNO_5$ requires:	C, 68.0;	H, 6.7;	N, 2.8%	

c) [1α(Z),2β,5α]-(±)-7-[2-(4-morpholinyl)-3-oxo-5-(2-propenyloxy)cyclopentyl]-4-heptenoic Acid
from Intermediate 12i. Purification by chromatography using 4:1 ER-PE (b.p. 60—80°) as eluent. IR ($CHBr_3$) 3500, 1735, 1705 cm^{-1}. TLC 4:1 ER-PE (b.p. 60—80°) Rf 0.28.

d) [1α(Z),2β,5α]-(±)-7-[2-(4-morpholinyl)-3-oxo-5-[(4-thien-2-yl)phenylmethoxy]cyclopentyl]-4-heptenoic Acid, Compound with Piperazine (2:1)
from Intermediate 12k. The acid was purified by chromatography using 1:99 methanol-$CHCl_3$ as eluent. The *title compound* (140 mg) precipitated from a solution of the acid (200 mg) and piperazine (100 mg) in ER. Crystallisation from EA gave material of m.p. 115° (dec). IR ($CHBr_3$) 1740 cm^{-1}. TLC ER Rf 0.7.

e) [1α(Z),2β,5α]-(±)-7-[2-(4-morpholinyl)-3-oxo-5-[[(1,1':4',1"-terphenyl)-4-yl]methoxy]cyclopentyl]-4-heptenoic Acid
m.p. 105° (dec.) from Intermediate 12l). Purification initially by chromatography using ether as eluent and then by crystallisation from ER-isopentane at 0°. TLC 9:1 ER-methanol Rf 0.23.

f) [1α(E),2β,5α]-(±)-7-[5-[[4'-methyl(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid
m.p. 80—85° from Intermediate 25a. Purification initially by chromatography using ER as eluent and then by crystallisation from ER-isopentane at —20°.

Analysis Found:	C, 73.1;	H, 7.7;	N, 2.8	
$C_{30}H_{37}NO_5$ requires:	C, 73.3;	H, 7.6;	N, 2.9%.	

g) [1α(E),2β,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid
m.p. 103—105° from Intermediate 25b. Purification initially by chromatography using ER as eluent and then by crystallisation from ER at —20°.

Analysis Found:	C, 72.8;	H, 7.7;	N, 3.0	
$C_{29}H_{35}NO_5$ requires:	C, 72.9;	H, 7.4;	N, 2.9%	

h) [1α(Z),2β,5α]-(±)-9-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-6-nonenoic Acid
m.p. 83—84° from Intermediate 12m. Purification initially by chromatography using ER as eluent and then by crystallisation from ER-isopentane.

Analysis Found:	C, 73.3;	H, 7.7;	N, 2.8	
$C_{31}H_{39}NO_5$ requires:	C, 73.6;	H, 7.8;	N, 2.8%	

i) [1α(Z),2β,5α(E)]-(±)-7-[2-(4-morpholinyl)-3-oxo-5-[(3-phenyl-2-propenyl)oxy]cyclopentyl]-4-heptenoic Acid
m.p. 74.5—76° from Intermediate 12o. Purification by chromatography using ER as eluent.

Analysis Found:	C, 70.3;	H, 7.9;	N, 3.3	
$C_{25}H_{33}NO_6$ requires:	C, 70.2;	H, 7.8;	N, 3.3%	

j) [1α(Z),2β,5α]-(±)-7-[5-[[4'-methyl(1,1'-biphenyl)-4-yl]methoxy]-3-oxo-2-(4-thiomorpholinyl)cyclopentyl]-4-heptenoic Acid, S-dioxide
from Intermediate 12r. Purification by chromatography using 98:2 ER-methanol as eluent. IR ($CHBr_3$) 3500, 1740, 1710 cm^{-1}.

Analysis Found:	C, 66.5;	H, 7.1;	N, 2.2	
$C_{30}H_{37}NO_6S$ requires:	C, 66.8;	H, 6.9;	N, 2.6%	

k) [1α(Z),2β,5α]-(±)-7-[3-oxo-5-[4-(phenylmethyl)phenylmethoxy]-2-(4-thiomorpholinyl)cyclopentyl]-4-heptenoic Acid, S-dioxide
m.p. 126.5—128° (dec.) from Intermediate 12s. Purification by chromatography using ER as eluent. TLC 95:5 ER-methanol Rf 0.46.

l) [1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-oxo-2-(4-thiomorpholinyl)cyclopentyl]-4-heptenoic Acid, S-dioxide
from Intermediate 12t. Purification by chromatography using 98:2 ER-methanol as eluent. IR ($CHBr_3$) 3480, 1743, 1710 cm^{-1}.

Analysis Found:	C, 66.0;	H, 6.7;	N, 2.6	
$C_{29}H_{35}NO_6S$ requires:	C, 66.3;	H, 6.7;	N, 2.7%	

m) [1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(hexahydro-1,4-oxazepin-4-yl-3-oxocyclopentyl]-4-heptenoic Acid
from Intermediate 12u. Purification by chromatography using ER as eluent. IR (Neat) 3500—2500 (br.), 1740, 1710 cm^{-1}. TLC ER Rf 0.47.

n) [1α(Z),2β,5α]-(±)-7-[5-[3-[(1,1'-biphenyl)-4-yl]propoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid
from Intermediate 12w. Purification by chromatography using ER as eluent. IR (Neat) 3700—2200 (br.), 1740, 1712 cm^{-1}. TLC ER Rf 0.25.

o) [1α(Z),2β,5α]-(±)-7-[5-[[3'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid
from Intermediate 12x. Purification by chromatography using ER as eluent. IR ($CHBr_3$) 3500, 1740, 1710 cm^{-1}. TLC ER Rf 0.2.

p) [1α(Z),2β,5α]-(±)-7-[5-decyloxy-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid
from Intermediate 12z. Purification by chromatography using 4:1 ER-PE as eluent, IR ($CHBr_3$) 3500, 1740, 1710 cm^{-1}. TLC (SiO_2) 4:1 ER-PE R_f 0.21.

Example 4
a) [1α(Z),2β,5α]-(±)-7-[5-(4-cyclohexylphenylmethoxy)-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid
A stirred solution of oxalyl chloride (0.612 ml) in dry toluene (5 ml) under nitrogen at —60° was treated dropwise with a solution of dry DMSO (0.5 ml) in dry toluene (5 ml) and the mixture stirred for 10 min. Simultaneously chlorotrimethylsilane (0.24 ml) was added dropwise to a solution of Intermediate 12e, (0.84 g) and triethylamine (0.264 ml) in dry toluene (10 ml) under nitrogen. This mixture was swirled for 5 min before being added dropwise to the above reaction mixture. The resulting solution was stirred at —60° for 15 min and then quenched with triethylamine (2.8 ml). The mixture was allowed to warm to 0°, poured into aqueous KH_2PO_4 (3.5 g in 200 ml water) and extracted with EA (4×50 ml). The combined organic extracts were washed with pH 6.5 phosphate buffer (2×20 ml), dried and concentrated. The residue was purified by chromatography on silica using 3:1 ER-PE as eluent to give the *title compound* as a gum (56 mg). IR ($CHBr_3$) 3500, 1740, 1710 cm^{-1}. TLC 80:1 ER-acetic acid Rf 0.39.
The following compounds were prepared using a similar procedure:

b) [1α(Z),2β,5α]-(±)-7-[2-(4-morpholinyl)-3-oxo-5(pentyloxy)cyclopentyl]-4-heptenoic Acid, Compound With Piperazine (2:1)
from Intermediate 12f. Purification of the acid by chromatography using ER as eluent. The *title compound* (212 mg) crystallised from a solution of the acid (271 mg) and piperazine (45 mg) in ER (10 ml) to give material of m.p. 99—102.5° (dec.).

Analysis Found:	C, 64.9;	H, 9.5;	N, 6.8	
$C_{23}H_{40}N_2O_5$ requires:	C, 65.1;	H, 9.5;	N, 6.6%	

c) [1α(Z),2β,5α]-(±)-7-[2-(4-morpholinyl)-3-oxo-5-[4-(phenylmethyl)phenylmethoxy]cyclopentyl]-4-heptenoic Acid, Compound With Piperazine (2:1)
m.p. 107—108 from Intermediate 12g.

Analysis Found:	C, 71.6;	H, 7.9;	N, 5.2	
$C_{32}H_{42}N_2O_5$ requires:	C, 71.9;	H, 7.9;	N, 5.2%	

d) [1α(Z),2β,5α]-(±)-7-[2-(4-morpholinyl)-3-oxo-5-[(4-phenylthien-2-yl)methoxy]cyclopentyl]-4-heptenoic Acid
m.p. 86—88° from Intermediate 12n.

Analysis Found:	C, 66.8;	H, 6.8;	N, 2.8	
$C_{27}H_{33}NO_5S$ requires:	C, 67.1;	H, 6.9;	N, 2.9%	

e) [1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-oxo-2-(1-piperidinyl)cyclopentyl]-4-heptenoic Acid, Compound With Piperazine (2:1)
m.p. 91—94° (dec.) from intermediate 33b. IR ($CHBr_3$) 1738 cm^{-1}.

f) [1α(Z),2β,5α]-(±)-7-[5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-3-oxo-2-(4-thiomorpholinyl)cyclopentyl]-4-heptenoic Acid, S-dioxide
from Intermediate 12q. Purification by chromatography using 98:2 ER-methanol as eluent. TLC 95:5 ER-methanol Rf 0.46. IR ($CHBr_3$) 3480, 1740, 1710 cm^{-1}.

g) [1α(Z),2β,5α]-(±)-7-[5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-3-oxo-2-(1-piperidinyl)cyclopentyl]-4-heptenoic Acid, Compound With Piperazine (2:1)
m.p. 68—76° (dec.) from Intermediate 12v. IR ($CHBr_3$) 1740 cm^{-1}.

Example 5
[1α(Z),2β,5α]-(±)-7-[5-[[4'-methyl(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid

A solution of Intermediate 18 (928 mg) in acetone (30 ml) was stirred with Jones reagent (2.67 M; 1.5 ml) at −5° to −3° for 40 min. Isopropanol (1.5 ml) was added and after stirring for 5 min, the mixture was poured into pH 6 phosphate buffer (100 ml) and extracted with ER (3×50 ml). The combined extracts were evaporated and the residue taken into ER and dried; evaporation of this ethereal solution gave a foam (840 mg) which was purified by chromatography on acid-washed silica gel (85 g) using ER as eluent. Crystallisation from ER-isopentane at 0° gave the *title compound* (0.26 g) of m.p. 98—102°. IR ($CHBr_3$) 3500, 1740, 1710 cm^{-1}.

Analysis Found:	C, 72.9;	H, 7.6;	N, 2.9	
$C_{30}H_{37}NO_5$ requires:	C, 73.3;	H, 7.6;	N, 2.9%	

Example 6
[1α(Z),2β,5α]-(±)-7-[5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid, Compound With Piperazine (2:1)

Jones reagent (0.883 ml, 2.7 M) was added to Intermediate 21 (600 mg) in acetone (25 ml) at −10° and stirred for 45 min at 10°. The mixture was neutralised by (25 ml) dropwise addition of 2N aqueous Na_2CO_3 and then poured into Na_2HPO_4/KH_2PO_4 buffer solution (pH 6). The mixture was extracted with CH_2Cl_2 (3×50 ml) and the combined extracts dried, filtered and evaporated. The residue was chromatographed on acid washed silica using 1:1 through to 3:1 ER-PE (b.p. 60—80°) as eluent to give an oil, which was dissolved in ER and treated with an excess of piperazine in ER to give the *title compound* as a solid (0.12 g), m.p. 116—117° (dec.).

Analysis Found:	C, 69.7;	H, 7.6;	N, 5.2	
$C_{32}H_{42}N_2O_6$ requires:	C, 69.8;	H, 7.7;	N, 5.1%	

Example 7
[1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid, Compound With Piperazine (2:1), Hemihydrate

To a solution of Example 1a (0.37 g) in dry ER (20 ml) was added piperazine (0.037 g) in dry ER (4 ml). The ER was decanted off and the residue crystallised from CH_2Cl_2-isopentane to give the *title compound* (0.2 g) m.p. 113—114°.

Analysis Found:	C, 70.9;	H, 7.7;	N, 5.4	
$C_{31}H_{40}N_2O_5 \cdot 1/4\ H_2O$ requires:	C, 70.9;	H, 7.7;	N, 5.4%	

Example 8
[1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid, Calcium (2+) (2:1), Monohydrate

Aqueous 0.2N.NaOH (2 ml) was added dropwise with stirring to a solution of Example 1a (0.25 g) in aqueous acetone (1:1), (10 ml) at room temperature until the pH reached 7.8. 7.2% w/v $CaCl_2$ (1 ml) was then added followed by water (10 ml) and stirring continued for 2 h. The solid was filtered off, washed with water (5 ml) followed by ER (10 ml) and dried (35°/0.05 mm Hg/7 h) to afford the *title compound* (0.163 g), m.p. 132—134°.

Analysis Found:	C, 69.1;	H, 6.8;	N, 2.6;	Ca, 3.9	
$C_{58}H_{68}N_2O_{10}Ca \cdot H_2O$ requires:	C, 68.9;	H, 7.0;	N, 2.8;	Ca, 4.0%	

Example 9
[1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid, Calcium (2+) (2:1), Trihydrate

Aqueous calcium acetate solution (0.17 g in 12 ml) was added dropwise with stirring to a solution of Example 1a) (0.6 g) and $NaHCO_3$ (0.106 g) in aqueous ethanol (1:1, 24 ml). The mixture

was stirred for 30 min when the solid was filtered off, washed with water (10 ml) followed by ER (5 ml) and dried (45°/200 mm Hg/4 h) to afford the *title compound* (0.56 g), m.p. 135° (dec.).

Analysis Found:	C, 66.2;	H, 6.9;	N, 2.6;	Ca, 3.6
$C_{58}H_{68}N_2O_{10}Ca \cdot 3H_2O$ requires:	C, 66.5;	H, 6.9;	N, 2.7;	Ca, 3.8%

Example 10

[1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid, Compound With N,N-dimethylpiperazine (2:1)

A solution of Example 1a) (0.35 g) in ER (25 ml) was treated with a solution of N,N-dimethylpiperazine (0.084 g) in ER (5 ml) and the mixture was allowed to stand in the cold. The *title compound* was filtered off and dried (0.33 g), m.p. 106—108°.

Analysis Found:	C, 71.9;	H, 7.9;	N, 5.1
$C_{32}H_{42}N_2O_5$ requires:	C, 71.9;	H, 7.9;	N, 5.2%

Example 11

a) [1R-[1α(Z),2β,5α]]-(−)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid

Jones reagent (1.83 ml, 2.67 M) was added to a stirred mixture of 'hyflo' (4.8 g) and the free base of Intermediate 47 a) (1.2 g) in acetone (40 ml) at 5° and stirring was continued for 40 min. Isopropanol (1.8 ml) was added dropwise and after 10 min the hyflo was removed by filtration and was washed with acetone (30 ml) and pH 5 buffer (50 ml, KH_2PO_4 and Na_2HPO_4 in water). The combined filtrates were evaporated *in vacuo* at 10—15° to remove most of the acetone. The residue was diluted with pH 5 buffer (25 ml) and extracted with ER (4×50 ml). The combined extracts were eashed with pH 5 buffer (20 ml) and brine (20 ml), then dried and evaporated to give an oil. The oil was chromatographed on silica using ER as eluent to give a solid (0.58 g) which was recrystallised from 2:1 ER-isopentane (15 ml) to give the *title compound* (0.484 g), m.p. 86—88°. $[\alpha]_D^{21.5}$=−13.66° ($CHCl_3$).

Analysis Found:	C, 72.5;	H, 7.5;	N, 2.7
$C_{29}H_{35}NO_5$ requires:	C, 72.9;	H, 7.4;	N, 2.9%

The following compound was prepared starting from Intermediate 35, in a similar manner to the preparation of the 1R compound:

b) [1S-[1α(Z),2β,5α]]-(+)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid

m.p. 81—84°.

Analysis Found:	C, 72.8;	H, 7.3;	N, 2.7
$C_{29}H_{35}NO_5$ requires:	C, 72.9;	H, 7.4;	N, 2.9%

Example 12

[1α(Z),2β,5α]-(±)-7-[2-(4-morpholinyl)-3-oxo-5-[(2-phenylthien-4-yl)methoxy]cyclopentyl]-4-heptenoic Acid

A solution of DMSO in dry toluene (1.46 ml, 1.41M) was added dropwise to a solution of oxalyl chloride in dry toluene (1.8 ml, 1.15 M) at −70° under nitrogen and the mixture stirred for 15 min. Simultaneously, a solution of Intermediate 50 (0.4 g) in dry toluene (4 ml) was treated with a solution of triethylamine in dry toluene (1.13 ml, 0.8 M) followed by a solution of trimethylsilyl chloride in dry toluene (1.07 ml, 0.085 M). After stirring at room temperature for 10 min the mixture was added to the above prepared solution of activated DMSO and stirring continued for 30 min. Triethylamine (2 ml) in toluene (5 ml) was added and after a further 30 min the mixture was treated with 1M aqueous KH_2PO_4 (20 ml) and extracted with ether (3×20 ml). The combined extracts were washed with water (50 ml), brine (30 ml) and then dried. After evaporation *in vacuo* the residue was chromatographed on silica using 2:1 EA-PE (b.p. 60—80°) as eluent to give the *title compound* as a solid (0.27 g). Crystallisation from ER-isopentane at −10° gave material of m.p. 52—55°. IR ($CHBr_3$) 3500, 1735, 1703 cm^{-1}.

Example 13

[1R-[1α(Z),2β,5α]]-(−)-7[5-[[1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic Acid, Calcium (2+) (2:1), Dihydrate

Aqueous calcium acetate solution (0.083 g in 4.8 ml) was added dropwise with stirring to a solution of Example 11 (0.25 g) and $NaHCO_3$ (40 mg) in aqueous ethanol (1:1, 9.6 ml). The mixture was stirred at room temperature for 2 h when the solid was filtered off, washed with water and dried (20°/0.1 mm Hg/20 h) to afford the *title compound* (0.23 g), m.p. 129—131°. $[\alpha]_D^{21}$=−28.47° ($CHCl_3$).

Analysis Found: C, 67.4; H, 6.8; N, 2.7; Ca, 3.5
$C_{58}H_{68}N_2O_{10}Ca \cdot 2H_2O$ requires: C, 67.7; H, 7.0; N, 2.7; Ca, 3.9%

Pharmaceutical Examples

Tablets

These may be prepared by direct compression or wet granulation. The direct compression method is preferred but may not be suitable in all cases as it is dependent upon the dose level and physical characteristics of the active ingredient.

A. Direct Compression	*mg/Tablet*
Active Ingredient	100.00
Microcrystalline cellulose B.P.C.	298.00
Magnesium stearate	2.00
Compression weight	400.00

The active ingredient is sieved through a 250 m^{-6} sieve, blended with the excipients and compressed using 10.0 mm punches. Tablets of other strengths may be prepared by altering the compression weight and using punches to suit.

B. Wet Granulation	*mg/Tablet*
Active ingredient	100.00
Lactose B.P.	238.00
Starch B.P.	40.00
Pregelatinised maize starch B.P.	20.00
Magnesium stearate B.P.	2.00
Compressed weight	400.00

The active ingredient is sieved through a 250 m^{-6} sieve and blended with the lactose, starch and pregelatinised starch. The mixed powders are moistened with purified water, granules are made, dried, screened and blended with the magnesium stearate. The lubricated granules are compressed into tablets as described for the direct compression formulae.

The tablets may be film coated with suitable film forming materials, e.g. methyl cellulose or hydroxylpropyl methyl cellulose using standard techniques. Alternatively the tablets may be sugar coated.

Capsules	*mg/Capsule*
Active ingredient	100.00
*STA-RX 1500	99.00
Magnesium stearate B.P.	1.00
Fill weight	200.00 mg

*A form of directly compressible starch supplied by Colorcorn Ltd., Orpington, Kent.

The active ingredient is sieved through a 250 m^{-6} sieve and blended with the other materials. The mix is filled into No. 2 hard gelatin capsules using a suitable filling machine. Other doses may be prepared by altering the fill weight and if necessary changing the capsule size to suit.

Inhalation Cartridges	*/Cartridge*
Active ingredient (micronised)	3 mg
Lactose B.P. to	25 mg

The active ingredient is micronised so that the majority of the particles are between 1 m^{-6} and 5 m^{-6} in longest dimensions and none are greater than 10 m^{-6}. The active ingredient is then blended with the lactose and the mix is filled into No. 3 hard gelatin capsules using a suitable filling machine.

Suspensions	*mg/5 ml Dose*
Active Ingredient	100.0
Aluminium monostearate	75.0
Sucrose (powdered)	125.0
Flavour, Colour	as required
Fractionated coconut oil to	5.00 ml

The aluminium monostearate is dispersed in about 90% of the fractionated coconut oil. The resulting suspension is heated to 115°C while stirring and then cooled. The flavour and colour are added and the active ingredient and sucrose are suitably dispersed. The suspension is made up to volume with the remaining fractionated coconut oil and mixed.

Injection for Intravenous Administration

Active ingredient	50 mg
Suitable vehicle to	5 ml

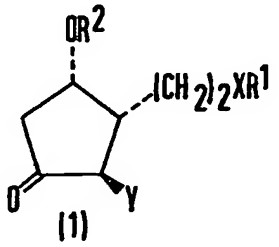
A sterile presentation of the active ingredient in an ampoule or vial together with an ampoule containing a suitable vehicle. The former may be prepared by (a) filling sterile material into vials under aseptic conditions (b) freeze drying a sterile solution of the active ingredient under aseptic conditions.

The vehicle may be (a) Water for Injections B.P. (b) Water for Injections B.P. containing: (1) Sodium chloride to adjust the tonicity of the solution and/or (2) buffer salts or dilute acid or alkali to facilitate solution of the active ingredient.

The vehicle is prepared, clarified and filled into appropriate sized ampoules sealed by fusion of the glass. The vehicle is sterilised by heating in an autoclave using one of the acceptable cycles.

Claims

1. Compounds of the general formula (1)



(1)

wherein

X is cis or trans —CH=CH—;

R^1 is straight or branched C_{1-7} alkyl bearing as a terminal substituent —$COOR^3$ where R^3 is a hydrogen atom, C_{1-6} alkyl or C_{7-10} aralkyl;

Y represents a saturated heterocyclic amino group which has 5 to 8 ring members and (a) optionally contains in the ring —O—, —S—, —SO_2—, —NR^4 (where R^4 is a hydrogen atom, C_{1-7} alkyl or aralkyl having a C_{1-4} alkyl portion; and/or (b) is optionally substituted by one or more C_{1-4} alkyl groups;

R^2 is (i) C_{2-4} alkanoyl; (ii) C_{3-6} alkenyl, optionally substituted by phenyl (the phenyl being optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy, halogen, C_{5-7} cycloalkyl or phenyl (C_{1-4}) alkyl), biphenyl (optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy or halogen), or naphthyl; (iii) C_{1-12} alkyl; (IV) C_{1-5} alkyl substituted by (a) phenyl [optionally substituted by halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-4} hydroxyalkoxy, trifluoromethyl, cyano, aryloxy, C_{5-7} cycloalkyl, aralkoxy, dimethylaminomethyl, carboxamido (—$CONH_2$), thiocarboxamido (—$CSNH_2$), C_{1-4} alkanoyl, —NR^5R^6 (where R^5 and R^6 are the same or different and are each a hydrogen atom or C_{1-4} alkyl, or where —NR^5R^6 is a saturated heterocyclic amino group as defined above for Y), C_{1-3} alkylthio, C_{1-3} alkylsulphinyl, C_{1-3} alkylsulphonyl, phenylalkyl having a C_{1-3} alkyl portion, aminosulphonyl, C_{1-3} alkanoylaminosulphonyl, phenylsulphonyl (the phenyl portion being optionally substituted by C_{1-3} alkyl or C_{1-3} alkoxy), nitro, or thienyl], (b) thienyl or furanyl (the thienyl and furanyl groups being optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, aryl or phenyl (C_{1-3}) alkyl or phenyl (C_{1-3}) alkoxy (the aryl or phenyl group in each case being optionally substituted by C_{1-3} alkyl, C_{1-3} alkoxy or halogen), aryloxy, C_{5-7} cycloalkyl, halogen, nitro or thienyl], (c) biphenyl (optionally substituted by phenyl or one or two C_{1-4} alkyl, C_{1-4} alkoxy, halogen substituents), or (d) naphthyl (optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy or halogen); and the physiologically acceptable salts and the solvates thereof.

2. Compounds as claimed in Claim 1 in which Y is morpholino, dioxothiamorpholino, homomorpholino, thiamorpholino or piperidino.

3. Compounds as claimed in Claim 1 or Claim 2 in which X is cis —CH=CH—.

4. Compounds as claimed in any one of the preceding claims in which R^1 is —$(CH_2)_2COOR^3$ where R^3 is a hydrogen atom or C_{1-3} alkyl.

5. Compounds as claimed in any one of the preceding claims in which R^2 is phenyl (C_{1-3}) alkyl in which the phenyl group is substituted by C_{1-3} alkylthio, thienyl, or phenyl (optionally substituted by C_{1-3} alkyl, C_{1-3} alkoxy, halogen or phenyl); phenylthienyl (C_{1-3}) alkyl; or cinnamyl.

6. Compounds as claimed in Claim 5 in which R^2 is phenyl (C_{1-3}) alkyl in which the phenyl group is substituted by phenyl, C_{1-3} alkylphenyl, C_{1-3} alkoxyphenyl or halophenyl; phenylthienyl (C_{1-3}) alkyl; or cinnamyl.

7. Compounds as claimed in Claim 1 in which:
X is cis —CH=CH—;
R^1 is $—(CH_2)_2COOH$;
Y is morpholino or piperidino;
R^2 is phenyl (C_{1-3}) alkyl in which the phenyl group is substituted by phenyl, C_{1-3} alkylphenyl, C_{1-3} alkoxyphenyl or halophenyl; phenylthienyl (C_{1-3}) alkyl; or cinnamyl;
and the physiologically acceptable salts and solvates thereof.

8. Compounds as claimed in any of the preceding claims in which the carbon atom carrying the $—(CH_2)_2XR^1$ group is in the R-configuration.

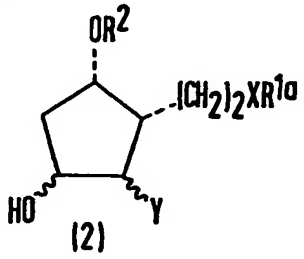
9. Compounds as claimed in Claim 1, said compounds being [1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid and the physiologically acceptable salts and solvates thereof.

10. Compounds as claimed in Claim 1, said compounds being [1R-[1α(Z),2β,5α]]-(—)-7-[5-[[(1,1'-biphenyl-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid and the physiologically acceptable salts and solvates thereof.

11. The calcium salts of the compounds claimed in Claims 9 and 10.

12. A pharmaceutical composition comprising a compound as claimed in any one of the preceding claims together with one or more pharmaceutical carriers.

13. A process for the preparation of a compound as claimed in Claim 1 which comprises:
(a) oxidising a compound of formula (2)



(2)

in which R^{1a} is a straight or branched alkyl group substituted by $—COOR^3$, $—CH_2OH$ or —CHO;
(b) in the preparation of a compound in which R^3 is alkyl or aralkyl, esterifying the corresponding compound in which R^3 is a hydrogen atom;
(d) reducing a corresponding compound in which X is an acetylene group; or
(e) in the preparation of a salt, treating a compound as claimed in Claim 1 with an acid or (where R^3 is a hydrogen atom) with a base, or converting one salt into another by exchange of cation.

14. Compounds as claimed in Claim 1, said compounds being the title compounds of any one of the Examples herein.

15. A pharmaceutical composition comprising a compound as claimed in any one of Claims 9 to 11 together with one or more pharmaceutical carriers.

16. A pharmaceutical composition as claimed in Claim 15 in unit dosage form.

17. A pharmaceutical composition substantially as described in any one of the pharmaceutical examples herein in which the active ingredient is a compound as claimed in any one of Claims 9 to 11.

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